IMPACT OF ANTIPSYCHOTIC DRUGS ON WEIGHT AND MONITORING OF ASSOCIATED CARDIOMETABOLIC OUTCOMES IN ADOLESCENTS

by

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ABSTRACT

The objective of the dissertation was to assess 1) trends in prevalence of overweight and obesity among adolescents (12-19 years), 2) frequency and predictors of regular monitoring of metabolic parameters as recommended by the American Diabetes Association (ADA)/ American Psychiatric Association (APA) guidelines among adolescents, and 3) association of second-generation antipsychotics (SGAs) prescriptions with changes in weight, among adolescents on antipsychotics compared to an age and gender matched randomly selected untreated comparison group. An ecologic study for the first objective and retrospective cohort studies for the second and third objective were conducted using a United States national electronic medical records database. Prevalence of overweight and obesity was assessed among exposed and comparison group adolescents during each calendar quarter between years 2000 and 2009. Frequency and predictors of regular monitoring of metabolic parameters were assessed in the second objective using multivariate logistic regression adjusting for covariates. Multivariate linear regression was used in the third objective to assess the percent change in follow-up body mass index (BMI) from baseline among antipsychotic users compared to the comparison group controlling for covariates. Adolescents on antipsychotics had higher prevalence of overweight and obesity than nonusing adolescents. The trend of prevalence of overweight and obesity among male antipsychotic users decreased while the trend of prevalence increased for female antipsychotic users compared to an untreated

comparison group respectively. The majority of adolescents on antipsychotics were under-monitored for BMI, lipids and glucose levels. Antipsychotic users with preexisting and newly diagnosed metabolic conditions were more likely to be regularly monitored for metabolic parameters than antipsychotic users without such conditions. Treatment with second-generation antipsychotics was associated with significant increase in BMI among adolescents relative to a matched comparison group. Antipsychotic treatment may have differential impact on weight gain in adolescent males and females. Strategies to increase awareness and adherence to ADA/APA guidelines in monitoring metabolic parameters among primary care physicians need to be developed. Weight gain among adolescents on antipsychotics needs to be controlled, or there may be increased use of limited health resources to treat obesity-related diseases in addition to mental health issues when these adolescents become adults.

I would like to dedicate my dissertation to my mother Sushama R. Ghate and my father Dr. Ravindra V. Ghate who have motivated and supported my aspirations of accomplishing a doctoral degree.

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CHAPTER I

INTRODUCTION

Introduction of antipsychotics

Antipsychotic agents are commonly used in the treatment of psychotic disorders, bipolar disorder, and nonpsychotic disorders. Clozapine was approved by United States Food and Drug Administration (FDA) for the treatment of schizophrenia in 1989, risperidone in 1993, olanzapine in 1996, quetiapine in 1997,[1] aripiprazole in 2001. First generation antipsychotics (FGAs), shortly after their introduction, were shown to suppress the acute symptoms of psychotic disorders and prevent their recurrence.[2] However, many patients with chronic disorders were found to be unresponsive to these antipsychotic drugs. In general, these drugs were found to be inadequate in affecting the long-term course of psychotic disorders and in improving outcomes.[3] Moreover, FGAs have been found to be associated with neurological disorders, such as acute extrapyramidal side effects (EPS) and tardive dyskinesia (TD).[4] The picture started to change with the advent of the second-generation antipsychotics (SGAs). This class of drugs is understood to have a significantly lower risk of the above-mentioned side effects.[5] A list of FGAs and SGAs is available in Table 1.

Although SGAs are associated with relatively lower side effects, they have been noted for their potential of causing metabolic disturbances including obesity, dyslipidemia and diabetes, leading to metabolic syndrome.[6] Cardiometabolic adverse effects in adolescents and children are of concern during development because they increase the risk of adult obesity, the metabolic syndrome, cardiovascular morbidity, and possibly malignancy.[7-10] Weight gain as a result of antipsychotic medications can cause a particular problem in these adolescents since their self-esteem is already decreased due to coping with their mental illness, and weight gain can make that worse.[11] Weight gain is not only an issue of self-esteem; it can also create an increased risk of hypertension, coronary artery disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, cancer, type II diabetes and hyperlipidemia.[11]

Prevalence of antipsychotic use in children and adolescents

Antipsychotic medications are increasingly prescribed to children and adolescents in the United States as first line treatment for psychotic disorders, bipolar disorder, and nonpsychotic mental disorders.[12] A study conducted by Curtis et al. estimated the 1 year prevalence of atypical antipsychotic use by age and sex among commercially insured youths in the United States.[13] The authors reported that the annual prevalence of atypical antipsychotic use was 267.1 per 100,000 patients aged 19 years and younger. Compared to the total population, patients with at least one claim for an atypical antipsychotic were more likely to be male (71% vs. 51.2%, $p<0.001$) and were older (76.9% vs. 51.6% of patients aged 12-19 years, $p<0.001$). The period prevalence of atypical antipsychotic use

was nearly 3.5 times higher in boys than in girls. More than 25% of male patients with at least one prescription for antipsychotic were aged 9 years or younger.

Another study examined changes in the prevalence of antipsychotic medication use and the characteristic of antipsychotic users in the US population between 1996 and 2005[1]. According to the authors, SGA use has increased between 1996 and 2005. The population prevalence of SGA use increased almost sevenfold in 8 years; 0.15% of the population used SGAs in 1996-1997 compared to 1.06% in 2004-2005. A study conducted by Olfson et al. examined national trends and patterns in antipsychotic treatment of youth seen by physicians in office-based medical practice.[12] According to the authors, the estimated number of office-based visits by youth that included antipsychotic treatment increased from approximately 201,000 in 1993 to 1,224,000 in 2002. The number of visits that included antipsychotic treatment was significantly higher for male white non-Hispanic youth. Overall, 9.2% of mental health visits and 18.3% of visits to psychiatrists included antipsychotic treatment. From 2000 to 2002, 92.3% of visits with prescription of an antipsychotic included second-generation medication. The authors concluded that there was a sharp national increase in antipsychotic treatment among children and adolescents in office-based medical practice. A recently published study found that American children take antipsychotic medicines at about six times the rate of children in the United Kingdom.[14] The overall prevalence of use of all antipsychotics almost doubled from 0.39 to 0.77 users per 1000 patient years for patients 0 to 18 years of age. These results demonstrated a very different picture from the study by Olfson et al.[12] in the United States, which showed a six fold increase in antipsychotic treatment between 1992 and 2002.[12]

Antipsychotics and weight gain

Although SGAs are associated with relatively smaller number of side effects they have been noted for their potential of causing metabolic disturbances including obesity, dyslipidemia and diabetes.[11, 15, 16] Published clinical trials suggest an increased risk of weight gain among both preadolescent and adolescent populations, as a result of SGAs.[15, 16] Weight gain as a result of antipsychotic medications can cause a particular problem in these adolescents since their self-esteem is already decreased due to coping with their mental illness and weight gain can make that worse.[11] Only two observational studies have assessed the association between antipsychotics and weight gain among adolescents and children. The first study, a retrospective cohort study, evaluated Medicaid medical and pharmacy claims to identify factors associated with incident cardiovascular events and metabolic disturbance in children and adolescents treated with antipsychotics.[17] The study found that antipsychotic treatment was associated with 2.13 times increased likelihood of obesity (odds ratio [OR], 2.13), compared to the untreated cohort. One of the limitations of this study is the limited generalizability of South Carolina's Medicaid enrollees to the US population as the Medicaid population is usually sicker in general with more comorbidities than the commercially insured population.[18] The limitation of this study is that the actual impact of antipsychotic treatment on clinical values was not known from this study. The second observational study was a prospective cohort study conducted in 203 youths aged 4 to 19 years with 1 week or less of lifetime antipsychotic treatment assessed the association of SGA medications with body composition and metabolic parameters.[19] After a median of 10.8 weeks treatment with SGAs researchers reported that the mean weight increased by 8.5 kg with olanzapine, by 6.1 kg with

quetiapine, by 5.3kg with risperidone, and by 4.4 kg with aripiprazole compared with minimal weight change of 0.2 kg in the untreated comparison group. Limitations of this study included the short duration of treatment (12 weeks), small comparison group (n=20), and limited generalizability of results to the national population. The study reported absolute change in BMI from baseline to 12 weeks of treatment without adjusting for or matching the comparison group to the treatment group by gender. Therefore the study did not account for the gender-related difference in BMI.

Monitoring of metabolic parameters

Guidelines published by the American Diabetic Association (ADA)/ American Psychiatric Association (APA) recommend monitoring of patients on antipsychotics regularly. [6] An eight member panel developed these guidelines based on evidence from experts drawn from the areas of psychiatry, obesity, and diabetes including representatives from the United States Food and Drug Administration (FDA) and the pharmaceutical industry.[6] The ADA/APA guidelines recommend monitoring BMI at baseline, then at 4, 8, 12 weeks, and quarterly after initiating or changing atypical therapy. Blood pressure and fasting plasma glucose should be checked at baseline, 12 weeks, and then annually. Fasting lipid profile should be checked at baseline, 12 weeks, and then every 5 years if normal. A check of total triglycerides and cholesterol every three months during the first year of atypical use has also been suggested. In 2004, the FDA required all manufacturers of SGAs (atypical antipsychotics), such as Clozaril ® (clozapine), Risperdal ® (risperidone), Zyprexa ® (olanzapine), Seroquel ® (quetiapine), Geodon ® (ziprasidone), and Abilify ® (aripiprazole), to add a new warning to the drugs'

labels about the increased risk of hyperglycemia and diabetes.[20] In 2010, the FDA changed prescribing information for olanzapine, with recommendations that physicians consider the increased potential for weight gain, hyperlipidemia, and long-term risks in adolescents using the medication.[21]

Public health implications

The public health implications of pediatric and adolescent patients on antipsychotic drugs and its associated cardiometabolic adverse effects are substantial. At present, obesity is a serious health concern among all adolescents and children. Published studies using data from NHANES surveys (1976–1980 and 2003–2006) show that the prevalence of obesity for children aged 2–5 years increased from 5.0% to 12.4%. Prevalence of obesity for those aged 6–11 years increased from 6.5% to 17.0% and for those aged 12–19 years, prevalence increased from 5.0% to 17.6%.[22, 23] Children and adolescents who are obese are more likely to remain obese as adults.[24] A study published by Whitaker et al. found that approximately 80% of children who were overweight at aged 10–15 years were obese adults at age 25 years.[24] Another study found that 25% of obese adults were overweight as children.[25] The latter study also found that if overweight begins before 8 years of age, obesity in adulthood is likely to be more severe.

The costs of obesity, for the year 2000, in the United States were estimated at $117 million – $61 million due to direct healthcare costs (i.e., preventive, diagnostic, and treatment services for obesity and related diseases) and $56 million on indirect costs (i.e., wages lost because of illness or disability, and future earnings lost because of premature death).[26] Among children and adolescents, the annual cost of treating obesity-related

diseases has increased more than threefold, from $35 million in 1979-1981, to $127 million in 1997-1999.[27]

There are numerous factors that contribute towards childhood obesity. Published evidence shows that antipsychotic treatment in children and adolescents may be associated with cardiometabolic factors. Physicians need to do a careful cardiometabolic evaluation prior to prescribing antipsychotic medication in pediatric and adolescent populations. Also, there is need for regular monitoring and evaluation of cardiometabolic adverse effects in this population. Findings from the current study may be used to create awareness and educate physicians about the need for monitoring of metabolic parameters and the risk of weight gain in adolescent patients who are prescribed antipsychotics to prevent cardiometabolic adverse effects.

Gaps in literature

Treatment-associated weight gain, coupled with increased antipsychotic prescribing among adolescents in the United States, may impact the prevalence of overweight adolescents. There is a significant gap in the literature and no studies to date have assessed the trend of prevalence of overweight among adolescents stratified on antipsychotics use. Previous studies have addressed the short term impact , 12 weeks to 1 year, of antipsychotic treatment on weight gain. However, none of the studies have addressed the long term trend of weight gain over 10 years due to antipsychotic treatment adjusting for increasing trend of weight among normal adolescents. The results of this study will provide an estimate of the seriousness of the problem of obesity among adolescents possibly due to antipsychotic use.

Secondly, very little information exists in the literature regarding the monitoring of metabolic parameters in the national population with commercial insurance treated in a primary care setting. Most importantly, none of the studies to date have assessed the monitoring of BMI and blood pressure, specifically in adolescents on antipsychotics. The ADA/APA guidelines suggest that physicians need to do a careful review of baseline metabolic parameters before or as soon as initiating antipsychotic treatment. Previous studies have assessed the monitoring patterns of metabolic parameters among adults on antipsychotics, which have been relatively low in commercially insured populations.[28, 29] A study conducted by Haupt et al. in commercially insured adults found that 9% and 17% received lipid and glucose testing within 12 weeks of starting SGA medication.[28] Another study by Morrato et al. conducted using administrative data from two managed care plans reported that only 13% of adults had glucose and lipid testing within 6 months of starting antipsychotic medication.[29] The findings from a study conducted in veterans reported relatively better monitoring rates of 39% for lipids and 57% for glucose testing respectively within 6 months of initiating SGA therapy.[30] Only one study assessed the monitoring of metabolic parameters using Medicaid data specifically among adolescents. The authors reported that lipid and glucose testing was performed in 13% and 32% of children and adolescents occurring 30 days before through 180 days after initiating SGA treatment.[31] The results of this study may not be generalizable to the national population as the Medicaid population is usually sicker with more comorbidities than the commercially insured population.[18] None of the studies conducted in adolescents have assessed the monitoring of metabolic parameters prior to initiating antipsychotic treatment (baseline). Very little information exists regarding the predictors of regular

monitoring of metabolic parameters in adolescents treated with SGAs. It remains unknown whether demographic characteristics, insurance type, concomitant medication use, and baseline medical conditions in addition to antipsychotic use are associated with regular monitoring of metabolic parameters among adolescents. There are limited retrospective studies comparing the differential risk of weight gain associated with SGAs in the adolescent population. The observational studies that have been conducted so far have either used short duration of treatment or a small comparison group. A real world study that assesses the differential impact of SGAs on weight gain in adolescent population is warranted. The goal of the current study is to compare the change in BMI among adolescents within 1 year of initiating antipsychotic treatment to the change in BMI among an age- and gender-matched, randomly selected, untreated comparison group.

Table 1: List of FGAs and SGAs

First Generation Antipsychotics (FGAs)	Second Generation Antipsychotics (SGAs)
Prochlorperazine (Compazine)*	Olanzapine (Zyprexa)
Haloperidol (Haldol)	Quetiapine (Seroquel)
Thioridazine (Mellaril)	Aripiprazole (Abilify)
Chlorpromazine (Thorazine)	Risperidone (Risperdal)
Perphenazine (Trilafon)	Ziprasidone (Geodon)
Fluphenazine (Prolixin)	Paliperidone (Invega)
Thiothixene (Navane)	Iloperidone (Fanapt)
Loxapine (Loxitane)	Clozapine (Clozaril, Fazaclo)
Trifluoperazine (Stelazine, APO-Trifluoperazine)	
Mesoridazine (Serentil)	
Molindone (Moban)	

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CHAPTER II

TREND OF OVERWEIGHT AND OBESITY

Title: Trend of Overweight and Obese among Adolescent Antipsychotic Users and Non-Antipsychotic Users from 2000 to 2009

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Target Journal: Archives of Pediatric Adolescent Medicine

Abstract

Objective: To assess the trends in prevalence of overweight and obese among adolescents on antipsychotics compared to nonusing adolescents. **Design:** An ecologic study of calendar quarters from 2000–2009 was conducted using an electronic medical records database. **Setting:** Outpatient, primary care. **Main Exposure:** The exposure group included 13,552 observations contributed by male and female adolescents on antipsychotics over 38 calendar quarters while the comparison group consisted of 40,659 patients randomly age- and gender- matched (3:1) to the exposed group. **Outcome Measures:** The primary outcome variable was the prevalence of exposed and comparison group patients during each calendar quarter between years 2000 and 2009. Prevalence was defined as the proportion of exposed and comparison group patients with body mass index (BMI) at or above the 85^{th} or 95^{th} percentile, as defined by age- and gender-specific growth charts, over total number of exposed and comparison group in each calendar quarter. **Results:** The mean BMI of exposed males and females during the overall study period was significantly higher (25.99 and 27.48 kg/m^2) compared to the comparison group (24.43 and 25.14 kg/m^2) ($p<0.001$). The mean prevalence of overweight among exposed males (38.83% vs. 26.57%) and females (34.54% vs. 20.81%) was also significantly higher than the comparison group during the study period ($p<0.01$). Quarterly trend analysis indicated significant differences in prevalence between exposed and comparison group males for age-adjusted BMI ≥85 and ≥95 percentile ($p<0.01$) and age-adjusted BMI ≥95 percentile among females ($p<0.05$) from 2000 to 2009. **Conclusion:** Overall, adolescents on antipsychotics had higher prevalence of overweight and obese than nonusing adolescents. Prevalence of overweight and obese among male

and female antipsychotic users was higher compared to the nonusing male and female adolescents. The trend of prevalence of overweight and obese among male antipsychotic users decreased while the trend of prevalence increased for male nonusing adolescents. On the contrary, the trend of prevalence of overweight and obese among female antipsychotic users increased while the prevalence remained stable among female nonusing adolescents.

Background

The number of children who take medications for chronic diseases has increased dramatically in the United States in recent years.[1-3] Evidence suggests that the prevalence of metabolic syndrome phenotype among US adolescents increased from 4.2% in 1988-1992 to 6.4% in 1999-2000.[4] The prevalence of obesity increased significantly from 13.8% in 1999-2000 to 16.0% in 2003-2004.[5] There has been a sharp national increase in antipsychotic treatment prescribed for psychotic disorders, bipolar disorder, and nonpsychotic mental disorders in children and adolescents in the United States. [3] A study by Olfson et al. examining national trends and patterns in antipsychotic treatment of youth reported that 9.2% of mental health visits and 18.3% of visits to psychiatrists included antipsychotic treatment. From 2000 to 2002, 92.3% of visits with prescription of an antipsychotic included a second-generation antipsychotic (SGA).[3] The annual prevalence of SGA use was reported as 267.1 per 100,000 patients aged 19 years and younger. Published clinical trials point towards an increased risk of weight gain among both preadolescent and adolescent populations, as a result of SGAs.[6, 7] Previous studies have addressed the short term impact of antipsychotic treatment on weight gain.

However, none of the studies have addressed the long term trend of weight gain due to antipsychotic treatment adjusting for increasing trend of weight among normal adolescents. Weight gain in youth is not only an issue of self-esteem; it can also create an increased risk of hypertension, coronary artery disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, cancer, type II diabetes and hyperlipidemia.[8]

The public health implications of children and adolescent patients on antipsychotic drugs and its associated cardiometabolic adverse effects are substantial. At present obesity is a serious health concern among adolescents and children and antipsychotic use may exacerbate this problem. Published studies indicate that from 1976–1980 to 2003–2006, respectively, the prevalence of obesity for children aged 2–5 years increased from 5.0% to 12.4%, 6–11 years increased from 6.5% to 17.0%, and 12–19 years increased from 5.0% to 17.6%.[9, 10] The costs of obesity, for the year 2000, in the United States were estimated at $117 million – $61 million due to direct healthcare costs and $56 million in indirect costs.[11] Among children and adolescents, the annual cost of treating obesity-related diseases has increased more than threefold, from $35 million in 1979–1981, to $127 million in 1997–1999.[12]

Treatment-associated weight gain, coupled with increased antipsychotic prescribing among adolescents in the United States, may impact the prevalence of overweight adolescents. There is a significant gap in the literature and none of the studies to date have assessed the trend of prevalence of overweight among adolescents with or without antipsychotics. We hypothesized that increase in the prevalence of antipsychotic use increases the prevalence of overweight among adolescents on antipsychotics

compared to those not treated with antipsychotics overall and across time. The purpose of the study is to assess the overall and quarterly trends of prevalence of overweight and obese adolescents on antipsychotics compared to a stratified random matched comparison group from 2000 to 2009.

Methods

Data source

The General Electric (GE) Centricity electronic medical record (EMR) database was used for this study. The GE EMR database has data on approximately ten million patients. The GE EMR database is comprised of data submitted by more than 70 consortium member institutions located in more than 40 states. A variety of practice types are represented ranging from solo practitioners to community clinics, to academic medical centers and large integrated delivery networks. The resulting research database provides information reflective of the clinical data captured in the practice setting, including diagnoses, chief complaints, medication orders, medication lists (patient-reported prescription and over-the-counter drug use), laboratory orders and results, and biometric readings. Using this database, patients on antipsychotic treatment can be identified and change in body mass index (BMI) can be assessed. A study by Brixner et al. has used GE EMR database to assess the impact of antipsychotics on weight gain.[13]

Study design

An ecologic study design was used, which is a type of observational study that uses aggregate rather than individual-level data.[14] This study design was used so that

aggregated data by each calendar quarter can be analyzed for assessing trend of overweight and obese for each quarter from 2000 to 2009. Data were aggregated and analyzed by calendar quarters to increase the data time points in this study. A quarter was defined as a period of three consecutive calendar months: January 1– March 31; April 1– June 30; July1– September 30; and October 1– December 31.

Study population

Adolescent patients (12–19 years of age) with a documented physician office visit within the GE EMR database, denoted as activity, were eligible for inclusion in this study. The exposed group was comprised of adolescents with at least one prescription for any SGA or first generation antipsychotic (FGA) between the years January 2000 and July 2009. Even though the data was available until July 2010 the recruitment period ranged from January 2000 to July 2010 to allow 1 year follow-up period for patients with prescription in July 2009. Patients were assigned an index date which was their first prescription for any SGA or FGA in the GE EMR database. Subsequent prescriptions for any FGA or SGA after the index prescription were also identified. Only those prescriptions with documented activity at least 365 days post prescription date were retained so that each prescription had at least 365 days of follow up period available in the GE EMR database. Although a follow-up period of 365 days was chosen arbitrarily, it is a common practice to use 365 days follow-up period in retrospective observational studies. The index prescription and subsequent prescriptions were categorized to first, second, third, or fourth quarter of each year within the years 2000–2009 based on the month of their prescription date. Figure 1 shows the schematic of the study design. Only

first prescription per patient per quarter was included in this study and any subsequent prescriptions within the same quarter were excluded. This was done to ensure that each patient contributed only one observation per quarter and to prevent duplication of prevalence estimates within each quarter. Each patient was then followed for a period of 1 year from the date of prescription and all available BMI values 1 month after the prescription date within this time period were obtained. Only those patients with at least 12 months of documented activity from date of prescription and at least one BMI value 1 month after the prescription date within the follow up period were eligible for inclusion in this study. This was done to allow at least 1 month for change in BMI after antipsychotic prescription.

The comparison population was identified based on presence of an activity (medical visit or prescription) in the GE EMR database and no prescriptions for any antipsychotic medications. After identifying the comparison population, we used stratified random sampling from the population with 3:1 matching on age, gender, and calendar quarter of antipsychotic prescription in the database to identify the comparison group.

Excess weight for children and adolescents is defined based on the year 2000 CDC gender-specific BMI-for-age growth charts.[15] Children and adolescents with BMI between the 85th and 95th percentile are considered overweight and those at and beyond the 95th percentile are considered obese.[16] For patients with more than one BMI value in a year, the maximum value was selected for analysis. Gender-specific CDC growth charts were used to identify patients with follow-up BMI at or above the 85th or 95th percentile for each calendar quarter. The primary outcome variable for this study is the proportions

of exposure and comparison group patients with BMI at or above the 85th or 95th percentile by quarter.

Baseline medical conditions such as dyslipidemia, hypertension, obesity, hypothyroidism, schizophrenia, bipolar disorder, depression, type 2 diabetes, and mental illness may influence weight. This study was approved by the institutional review board at the University of Utah on September 24th 2010.

Analysis

Quarterly means and proportions for demographic characteristics such as age, race, geographic region, and insurance type were calculated and averaged for the study period. Similarly, mean proportion of concomitant medication use and baseline medical conditions was also evaluated for each quarter and averaged for the study period. Quarterly means were averaged for all quarters from January 2000–July 2009 to provide an estimate of distribution throughout the study period for exposed and unexposed groups. T tests with unequal variances were used to illustrate differences, if any, in the average demographic, concomitant medication use, and baseline medical conditions between the exposure and comparison group for the whole study period. The trend of age-and gender-stratified prevalence of subjects with BMI ≥85th and ≥95^{h} percentile was plotted for each quarter from 2000 to 2009 for the exposed and comparison groups. Lowess smoothing technique was used to smooth the trend of prevalence of BMI ≥85th and ≥95th percentile for exposed and comparison group for graphical comparisons.[17] Prevalence of subjects with BMI ≥85thand ≥95^{h} percentile for the exposed and comparison group males, females, and both sexes was assessed for the most recent single

year 2008–2009. Seemingly unrelated estimation test in STATA was used to compare the slope coefficients of age stratified prevalence of BMI ≥85thand ≥95th percentile separately for the exposed and comparison groups.[18]

All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC) and STATA Version 10.0 (StataCorp. 2007. *Stata Statistical Software: Release 10*. College Station, TX: StataCorp LP).

Results

The GE EMR database consisted of approximately 1.8 million patients 0-19 years old. Of these, 24,109 patients had at least one prescription for FGAs or SGAs and approximately 1.7 million had at least one documented activity in the GE database without a single prescription for antipsychotic agent. Of these, only 9,374 exposure group adolescents and 669,207 comparison group adolescents had at least one documented activity 12 months post index date. A total of 6,183 and 387,435 patients in the exposure and comparison group, respectively, had at least one follow-up BMI 1 month post index date/activity and were eligible for inclusion in this study (Figure 2). The exposed group (n=6,183) had multiple prescriptions for antipsychotic agents longitudinally in the GE EMR database with 8,128 observations contributed by males and 5,425 observations contributed by females assigned to respective quarters based on the date of prescription. The final comparison group consisted of a stratified random sample matched to the exposed group by distribution of gender, age, and calendar quarter [males (n=24,384) and females (n=16,275).

Table 2 presents the mean demographic and baseline medical conditions in the exposed and unexposed groups. The mean age was similar between the exposure and comparison group males and females respectively. The mean proportion of exposed males and females from the Midwest region was highest (41.16% and 37.01%) compared to the comparison group males (16.33% and 16.87%) respectively. The comparison group males and females had significantly higher proportion with commercial insurance ($p<0.01$). However, the exposure group males and females had significantly higher proportion with Medicaid insurance ($p<0.01$).

The mean BMI during the study period for both the exposed group males and females (Table 2) was significantly higher compared to the mean BMI of the comparison group males and females, respectively ($p<0.001$). The mean percentage of males with BMI $\geq 85^{th}$ and 95^{th} percentile (58.09% and 38.83%) from the exposure group was higher than the comparison group (46.49% and 26.57%) for the entire study period. The mean percentage of females with BMI $\geq 85^{th}$ and 95^{th} percentile (57.61% and 34.54%,) was slightly lower than males. However it was significantly higher compared to the female comparison group (42.62% and 20.81%). Both exposure group males and females had higher anticonvulsant use (18.93%). However, only the comparison group males had higher corticosteroid use (7.89%). Both exposure group males and females had a similar percentage of subjects with mental illness (37.29% and 37.16%), respectively which was significantly higher compared to the comparison group (13.73% and 13.61%). There were significant differences among other baseline medical conditions but the mean percentages were less than 10% in both exposure and comparison group.

The annual prevalence of BMI ≥85th (Figure 3) and ≥95th (Figure 4) percentiles in exposure and comparison group by gender were plotted for visual inspection and analysis of linear trend over time. Table 4 presents the trend analysis of BMI ≥ 85th and 95th percentile among exposure and comparison group adolescents by gender from 2000 to 2009. The proportion of males with BMI ≥85th and ≥95th percentile for the exposed group significantly decreased by 0.25% and 0.31%, respectively, for each quarter from 2000 to 2009 ($p<0.05$). On the contrary, the proportion of males with BMI ≥85th percentile for the comparison group increased by 0.09% for each quarter from 2000 to 2009 ($p<0.05$). The linear trends of BMI ≥85th and ≥95th percentile among the exposed and comparison group males were significantly different from each other ($p=0.001$ and $p=0.003$, respectively).

Among exposed females, significant increase of 0.35% was observed in the prevalence of BMI ≥95th percentile ($p=0.011$). The comparison group females did not show significant change in prevalence of BMI ≥85th and ≥95th percentile from 2000 to 2009. The linear trend of BMI ≥95th percentile among the exposed and comparison group females were significantly different from each other ($p=0.011$, respectively).

Prevalence estimates among adolescent male and female exposure and comparison group in 2008–2009 are shown in Table 3. The prevalence of overweight BMI was higher for exposure group females compared to the exposure group males. On the contrary, the prevalence estimates for obese comparison group males was higher than for females. Also, the magnitude of difference between the exposure and comparison group prevalence estimates was almost double in females compared to males.

Discussion

Overall, the prevalence of overweight and obese from 2000 to 2009 was found to be higher among male and female antipsychotic users compared to the male and female comparison group, respectively. However, the trend of overweight and obese adolescent male antipsychotic users was decreased while the trend of overweight and obese nonantipsychotic user males increased from 2000 to 2009. The decreasing trend in male antipsychotic users may be associated with better management of excessive weight gain or use of antipsychotics with lower potential for weight gain. Contrary to males, the trend in the prevalence of overweight and obese in female antipsychotic users increased while the trends for nonantipsychotic user females remained unchanged from 2000 to 2009. The increasing trend of prevalence of obesity observed in adolescent female antipsychotic users may be associated with the increased likelihood of excessive weight gain in females compared to males.[19-22] A study conducted by McIntyre et al. reported that girls 13 years or older exposed to antipsychotics had higher odds of obesity/excessive weight gain compared to boys.[22] Studies have shown that antipsychotics induce hyperprolactinemia in women which promotes appetite and insulin resistance.[23, 24] Increased prolactin levels may be associated with the increased likelihood of excessive weight gain among females.

The trend of prevalence of overweight and obesity among female comparison group remained stable and did not show statistically significant change. There may not be a significant difference in prevalence of overweight and obesity between each quarter to see a statistically significant difference in trend. Although not significant, the negative coefficients for the female comparison group may imply that the prevalence of BMI at or

above the 85th and 95th, percentile among adolescent females is decreasing over time. A decrease in prevalence of overweight and obese among nonusing females can be corroborated by the fact that the adolescent females had the lowest prevalence estimates for overweight and obesity in 2008–2009 compared to males. Societal pressure and peer pressure of being normal weight and the stigma attached with being overweight among adolescent females could be the reason for lower prevalence of high BMI in this age group.[25, 26]

In this study the proportion of males was higher than for females and the mean age of females was higher than the mean age of males. This is consistent with other studies where males were more likely to be prescribed an antipsychotic agent compared to females[27, 28] and female antipsychotic users tended to be older than males.[28] Males may be more likely to be prescribed antipsychotics compared to females because of the higher likelihood of excessive weight gain among females associated with antipsychotic use.

This study has several strengths. This study is the first to compare the prevalence of overweight and obesity in adolescent antipsychotic and nonantipsychotic users using a large national electronic medical record database over a long period of time (10 years). Another strength of this study is the use of a stratified random comparison group. Stratified random sampling ensured that the age and gender distribution was sufficiently represented in the comparison group. BMI is age and gender dependent. Therefore matching was performed based on age and gender in this study. Proper distribution of BMI and age allows appropriate comparison between exposure and random comparison group. Stratified random sampling also controlled for any seasonal influence on outcome.

The results of this study should be viewed in light of several limitations. This study used an ecologic study design. Therefore the potential for ecologic fallacy cannot be rejected. One of the most important limitations of the study is that prescriptions in an EMR database are tracked by prescription orders and medication lists and not by actual prescriptions filled at the pharmacy. We cannot be entirely sure if patients are filling the medications prescribed to them. Also, patients with at least one prescription order for antipsychotic drug were considered to be on the drug during the follow-up period. This may have resulted in misclassifying patients as antipsychotic user even if the patients were not actively or regularly taking the drug during the follow-up period. The results (proportion of overweight) may be biased towards the null because misclassified antipsychotic users who are not regularly taking antipsychotics may have very little impact on their weight. Another limitation of the database is that it is predominantly primary care physician network database and, therefore, health care received outside of the primary care setting may not be captured in the database. This dataset likely includes antipsychotic users who are relatively less severe as compared to those patients seeking care from psychiatrists or other mental health specialists. As a result the results may be biased towards the null since we are automatically excluding sicker or more severe patients.

The prevalence estimates of overweight and obesity for nonantipsychotic users provided in this study may be higher than the general population. A recent study by Ogden et al. estimated the prevalence of high BMI in US children and adolescents using the National Health and Nutrition Examination Survey (NHANES) database.[29] The prevalence estimates of overweight for adolescents of both sexes in 2007–2008 using

NHANES were lower compared to 2008-2009 prevalence estimates for current study (34.2% vs. 45.9% and 18.1% vs.25.24% for ≥85th and ≥95th percentile respectively). The GE EMR database used in the current study consists of patients with predominantly primary care visits and the comparison group included patients not on antipsychotics but with other medical conditions. This may have resulted in a selection bias and the patients in the comparison group may be sicker than individuals participating in the NHANES study and may not be appropriate controls. On the other hand, the results of the NHANES study may be biased towards the null because of the healthy volunteer effect.

Conclusions

Overall, adolescents on antipsychotics had higher prevalence of overweight than nonusing adolescents. The trend of prevalence of overweight and obese among male antipsychotic users decreased while the trend of prevalence increased for male nonusing adolescents. On the contrary, the trend of prevalence of obesity among female antipsychotic users increased while the prevalence remained stable among female nonusing adolescents. Antipsychotic treatment may have differential impact on weight gain in adolescent males and females or a disparity in monitoring metabolic parameters may exist between adolescent males and females. More research is needed that assesses the weight gain potential of antipsychotic treatment among adolescent males and females separately. Also, future studies should assess the monitoring patterns of metabolic parameters in adolescents treated with antipsychotics to assess if any disparity exists in monitoring metabolic parameters among males and females.

Table 2 Mean Demographic and Baseline Conditions in Exposure and Stratified Random Comparison Group Males 2-19 Years Old

	Exposure Group Males	Comparison Group Males		Exposure Group Females	Comparison Group Females	
	%	%	P value	%	%	P value
Age (Mean, SD)	14.86 (0.28)	14.86 (0.28)	1.000	15.98 (0.34)	15.98 (0.34)	1.000
Region						
Northeast	25.05	27.74	0.173	31.18	31.07	0.965
Midwest	41.16	16.33	0.000	37.01	16.87	0.000
South	23.87	37.77	0.000	21.33	34.05	0.000
West	9.94	18.17	0.000	10.48	18.04	0.000
Insurance Type						
Commercial	35.73	46.62	0.000	40.77	47.54	0.001
Medicare	4.28	0.37	0.000	2.62	0.13	0.000
Medicaid	24.14	3.84	0.000	17.77	4.81	0.000
Self-pay	3.76	2.49	0.239	3.06	3.14	0.884
Other/Unknown	3.76	2.49	0.374	3.06	3.14	0.884
BMI						
Avg. Quarterly BMI	25.99	24.43	0.000	27.48	25.14	0.000
BMI ≥85th percentile	58.09	46.49	0.000	57.61	42.62	0.000
BMI ≥95th percentile	38.83	26.57	0.000	34.54	20.81	0.000
Medications						
Beta Blockers	2.04	0.64	0.000	3.35	0.99	0.000
OAB Wt. Gain	0.89	2.76	0.000	0.57	2.74	0.000
OAB Wt. Loss	0.68	0.61	0.582	0.88	1.31	0.052
Antidepressants	3.24	1.04	0.001	4.26	1.57	0.000
Anticonvulsants	18.93	1.26	0.000	14.28	1.24	0.000
Corticosteroids	5.47	7.89	0.001	6.40	6.36	0.955
Anorexiants	0.12	0.02	0.008	0.15	0.18	0.537
Antiobesity	0.10	0.09	0.888	0.32	0.23	0.518
Oral Contraceptive	0	0		4.84	4.07	0.268
Baseline Conditions						
Dyslipidemia	0.67	0.23	0.004	0.29	0.19	0.240
Hypertension	0.89	0.54	0.090	0.68	0.35	0.021
Obesity	2.81	2.39	0.222	3.66	2.67	0.010
Hypothyroidism	0.73	0.25	0.005	1.31	0.57	0.002
Schizophrenia	1.13	0.00	0.000	0.92	0.00	0.000
Bipolar Disorder	6.75	0.27	0.000	8.14	0.29	0.000
Depression	2.15	0.71	0.002	3.15	1.05	0.000
Type 2 Diabetes	3.91	1.12	0.000	5.10	1.89	0.000
Mental Ilness^	37.29	13.73	0.000	37.16	13.61	0.000

^Mental Illness consists of ICD9 codes 290-319

Table 3 Prevalence of Overweight and Obese in Exposure Group and Comparison Group Aged 12-19 Years by Gender and Age, 2008-2009

	Exposure Group 12-19 y	**Comparison Group 12-19 y**	**Difference 12-19 y**
BMI ≥95th percentile			
Both Sexes	35.45%	25.24%	10.21%
Males	34.70%	27.62%	7.07%
Females	36.64%	21.43%	15.22%
BMI ≥85th percentile			
Both Sexes	56.32%	45.95%	10.37%
Males	54.91%	47.59%	7.31%
Females	58.58%	43.32%	15.27%

Table 4 Trend Analysis of BMI ≥85th and ≥95th Percentile Among Exposure Group and Comparison Group Adolescents by Gender, 2000-2009

Male 12-19 Years	**Coefficient (Prevalence)**	**95% Confidence Interval**		**P value**	**Chi Square Value**	**P value**
Comparison Group ≥85th Percentile	0.09	0.01	0.17	**0.021**	10.25	**0.001**
Exposure Group ≥85th Percentile	-0.25	-0.44	-0.06	**0.012**		
Comparison Group ≥95th Percentile	0.09	-0.03	0.20	0.155	8.76	**0.003**
Exposure Group ≥95th Percentile	-0.31	-0.55	-0.08	**0.009**		
Females 12-19 Years	**Coefficient (Prevalence)**	**95% Confidence Interval**		**P value**	**Chi Square Value**	**P value**
Comparison Group ≥85th Percentile	-0.05	-0.18	0.08	0.474	2.23	0.135
Exposure Group ≥85th Percentile	0.16	-0.08	0.39	0.190		
Comparison Group ≥95th Percentile	-0.01	-0.19	0.18	0.928	6.40	**0.011**
Exposure Group ≥95th Percentile	0.35	0.14	0.56	**0.001**		

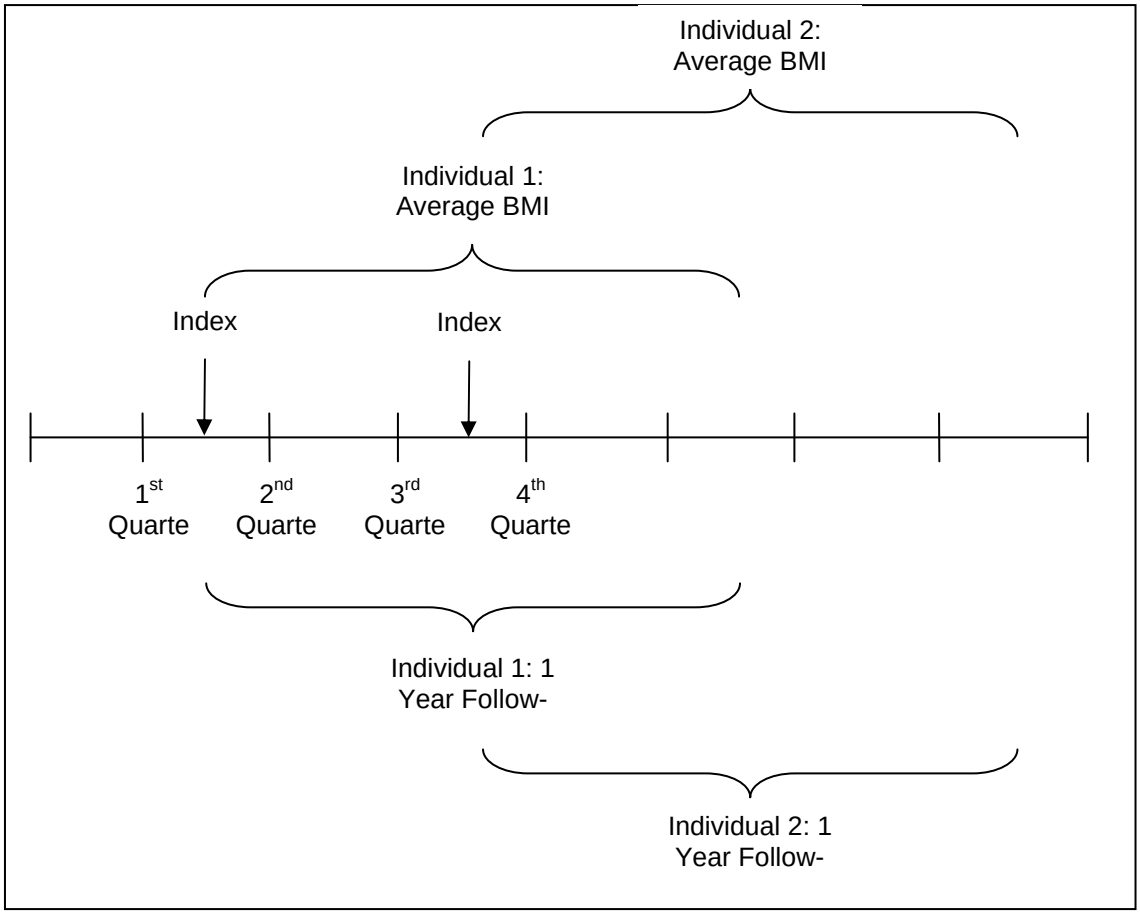

Figure 1 Schematic Representation of Study Design for Two Individuals

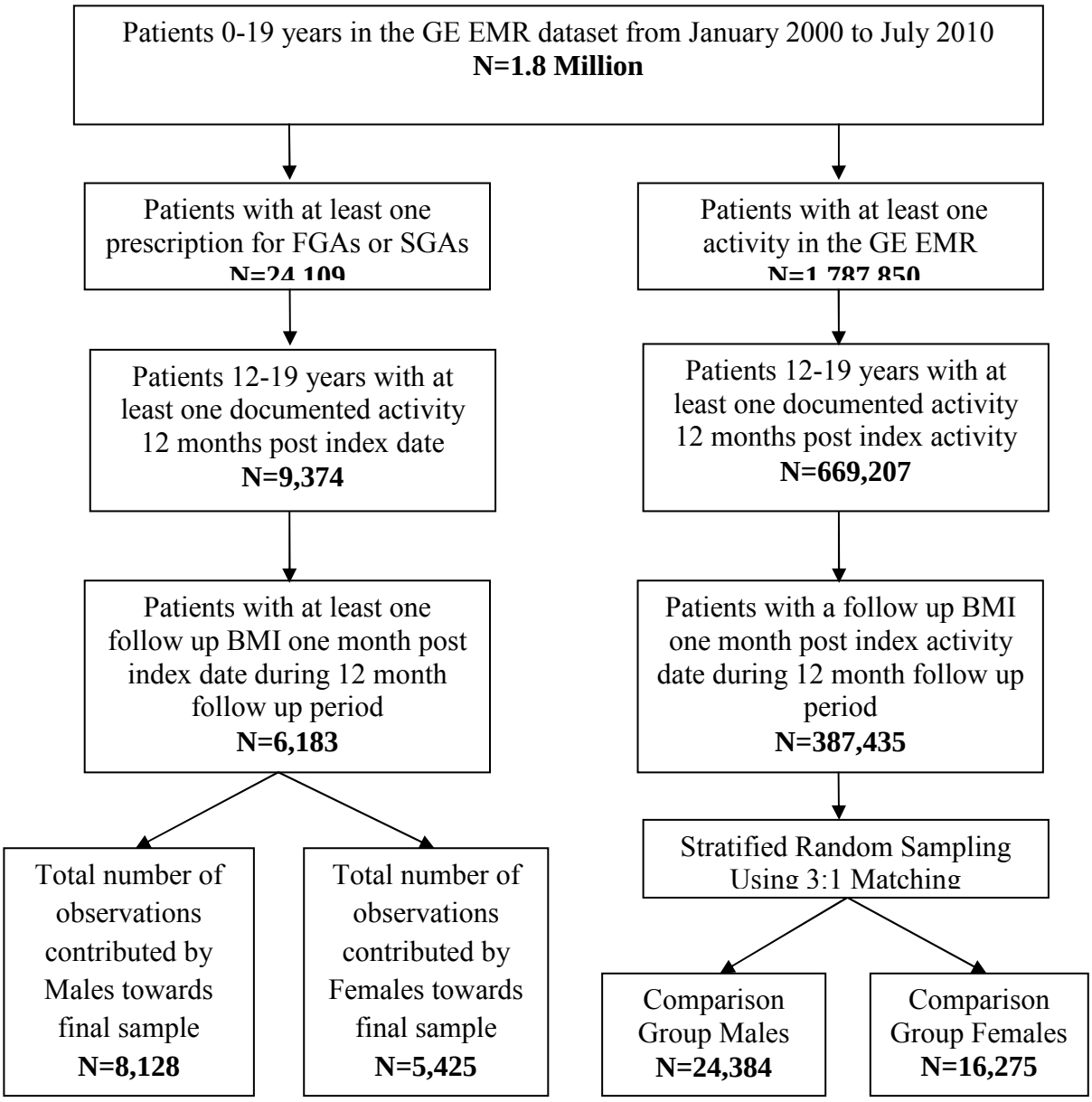

Figure 2 Flowchart of Patient Selection

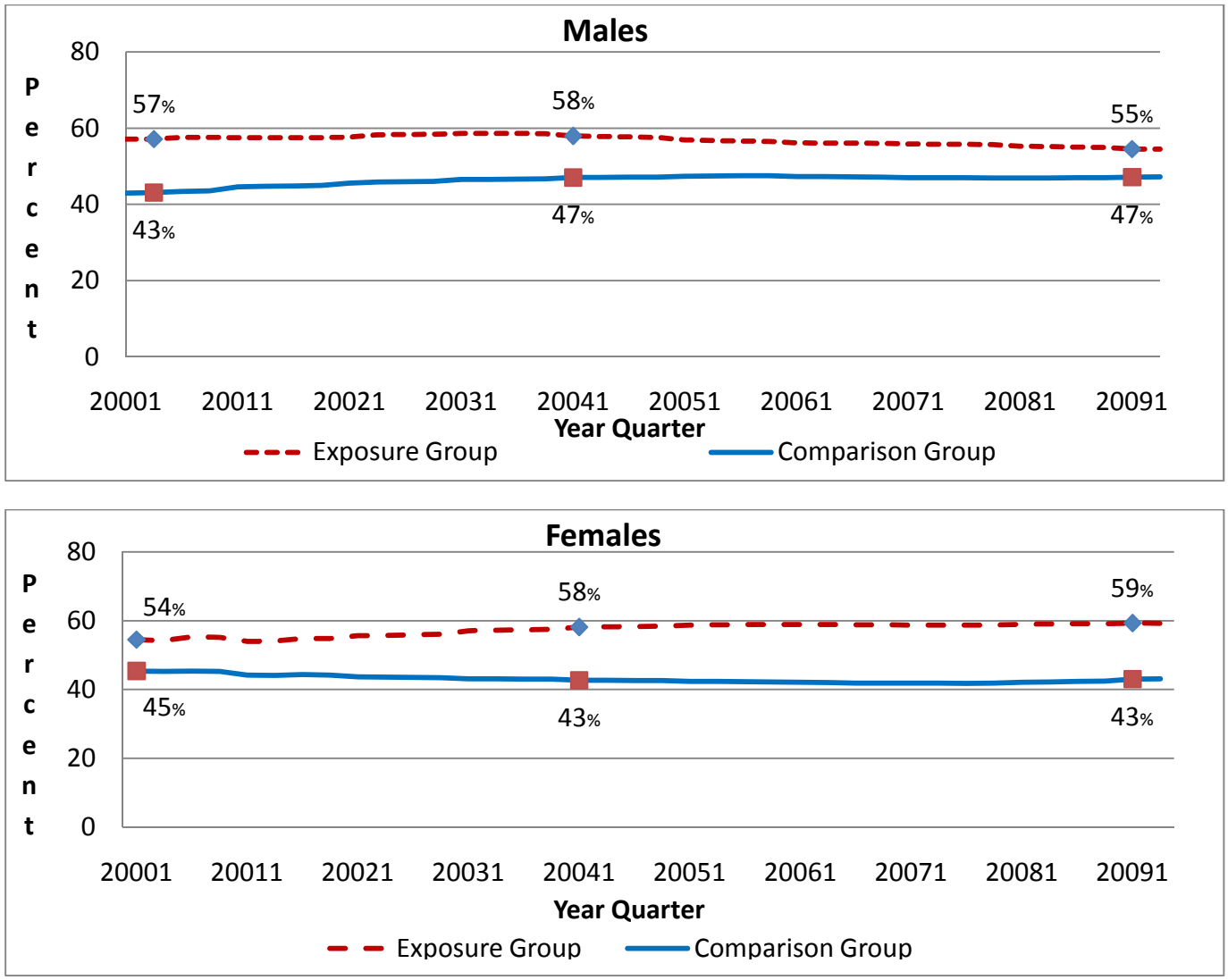

Figure 3 Percent of BMI ≥ 85th Percentile in Exposure and Comparison Group Males and Females Aged 12 Through 19 Years Old, 2000-2009

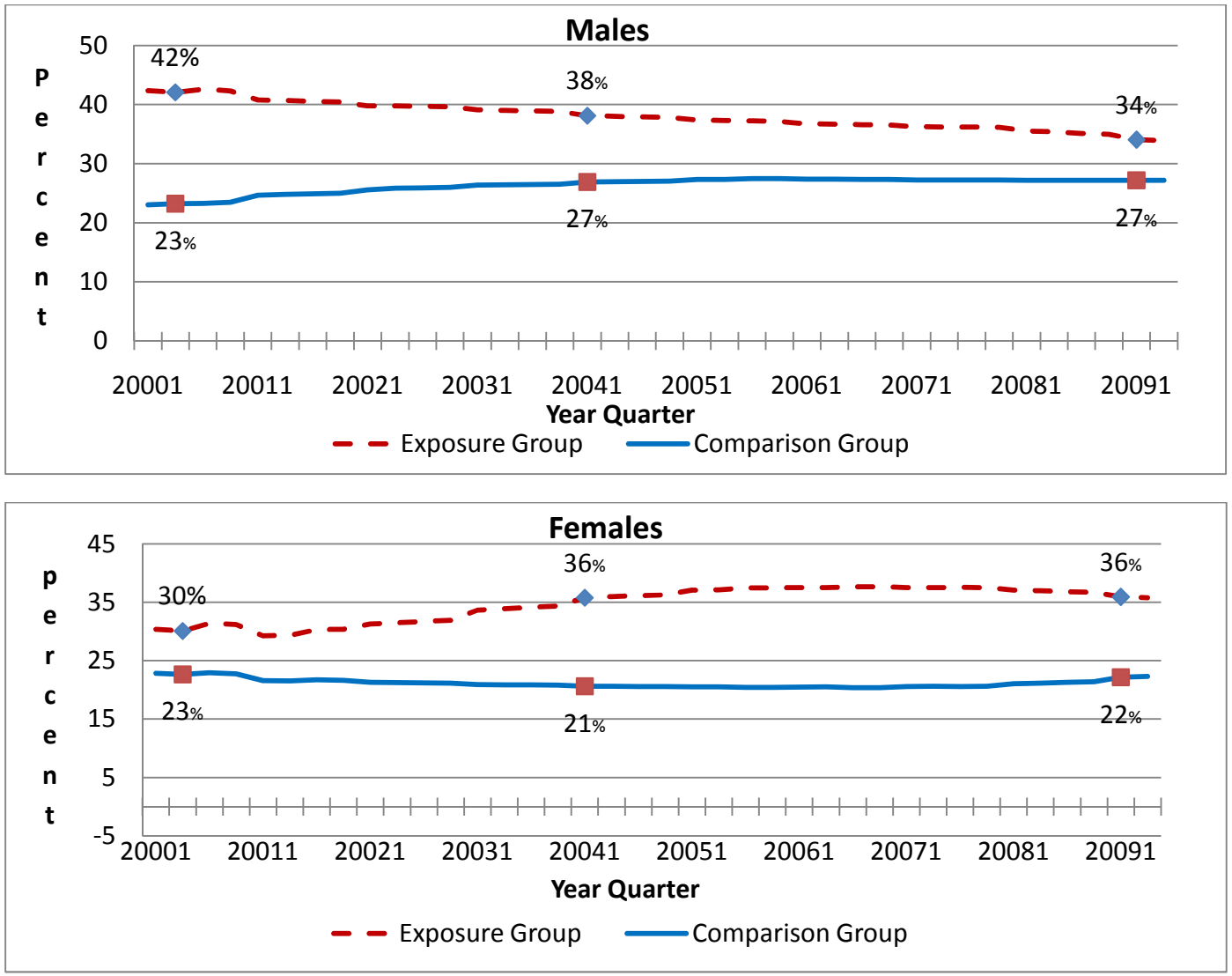

Figure 4 Percent of BMI ≥ 95th Percentile in Exposure and Comparison Group Males and Females Aged 12 Through 19 Years Old, 2000-2009

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CHAPTER III

FREQUENCY AND PREDICTORS OF METABOLIC MONITORING

Title: Predictors of Metabolic Parameter Monitoring in Adolescents on Antipsychotics.

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Target Journal: Journal of Psychiatry

Abstract

Objective: To assess the frequency and predictors of regular monitoring of metabolic parameters as recommended by the American Diabetes Association (ADA)/ American Psychiatric Association (APA) guidelines in adolescents (12–19 years old) receiving antipsychotic prescriptions compared to an age and gender matched comparison group. **Methods:** A retrospective cohort study was conducted using an ambulatory care electronic medical record database in the United States from January 2004 to July 2009. The exposure group consisted of adolescents with first prescription for SGAs (denoted as index date). The comparison group, selected from those without antipsychotics, was matched (3:1) to the antipsychotic medication group on age, gender, and month of index antipsychotic prescription. Baseline and follow-up metabolic measurements were assessed and patients were categorized as being regularly monitored if the frequency of measurements were as recommended by the ADA/ APA guidelines over the 395 day follow up. Multivariate logistic regression was conducted to assess the predictors of regular monitoring, adjusting for demographic characteristics, baseline medications, and baseline medical conditions. **Results:** The exposure and comparison group consisted of 3,038 and 9,114 subjects, respectively, (mean age 15.53 years, 54% males). The frequency of monitoring of BMI, lipids, total cholesterol, and fasting blood glucose as recommended by ADA/APA guidelines among antipsychotic users (25%, 55%, 1.7%, and 2%) was low but significantly higher compared to the matched comparison group (9.5%, 37.4%, 0.8%, and 0.8%, respectively) ($p<0.05$). Overall, antipsychotic treatment was associated with 1.5 to 4.26 fold increase in likelihood of metabolic monitoring compared to the comparison group ($p<0.05$). Other predictors of monitoring included oral

antidiabetic use for BMI monitoring (Odds Ratio [OR], 3.65; 95% confidence interval [CI], 2.19–6.08); high blood cholesterol levels for blood pressure (OR, 3.17; 95% CI, 2.02–4.08), total cholesterol (OR, 11.85; 95% CI 6.09–23.05), and fasting blood glucose (OR, 7.81; 95% CI, 3.62–16.86). **Conclusion:** We observed that the majority of adolescents on antipsychotics are under monitored for BMI, lipids and glucose levels. Antipsychotic users with preexisting and newly diagnosed metabolic conditions were more likely to be regularly monitored for metabolic parameters than antipsychotic users without such conditions. Without regular monitoring of metabolic parameters, adolescents on antipsychotics may grow into adulthood with abnormal weight and other metabolic parameters and impact adult obesity and its associated cardiovascular outcomes.

Background

Second generation antipsychotics (SGAs) are used as first line treatment for schizophrenia, [1] bipolar disorder, [2] and major depressive disorder.[3] The national trend of prescriptions for antipsychotics in adolescents has sharply increased in the United States. The annual number of visits that included antipsychotic prescription increased from 274.7 in 1993 to 1,438.4 in 2002 per 100,000 population younger than 21 years. [4] The American Diabetes Association (ADA)/ American Psychiatric Association (APA) guidelines, published in February 2004, recommend monitoring of metabolic parameters such as weight and body mass index (BMI), blood pressure, fasting plasma glucose, and fasting lipid profile for all patients receiving antipsychotic treatment regardless of age.[5] An eight-member panel developed these guidelines based on evidence from experts

drawn from the areas of psychiatry, obesity, and diabetes including representatives from the United States Food and Drug Administration (FDA) and the pharmaceutical industry.[5] In 2004, the FDA required all manufacturers of SGAs (atypical antipsychotics), such as Clozaril ® (clozapine), Risperdal ® (risperidone), Zyprexa ® (olanzapine), Seroquel ® (quetiapine), Geodon ® (ziprasidone), and Abilify ® (aripiprazole), to add a new warning to the drugs' labels about the increased risk of hyperglycemia and diabetes.[6] In 2010, the FDA changed prescribing information for olanzapine, with recommendations that physicians consider the increased potential for weight gain, hyperlipidemia, and long-term risks in adolescents using the medication.[7]

Previous studies have assessed the monitoring patterns of metabolic parameters among adults on antipsychotics which have been relatively low in commercially insured populations.[8, 9] A study conducted by Haupt et al. in commercially insured adults found that 9% and 17% received lipid and glucose testing within 12 weeks of starting SGA medication. Another study by Morrato et al. conducted using administrative data from 2 managed care plans reported that only 13% of adults had glucose and lipid testing within 6 months of starting antipsychotic medication.[9] The findings from a study conducted in veterans reported relatively better monitoring rates of 39% for lipids and 57% for glucose testing, respectively, within 6 months of initiating SGA therapy.[10] Only one study assessed the monitoring of metabolic parameters using Medicaid data specifically among adolescents. The authors reported that lipid and glucose testing was performed in 13% and 32% of children and adolescents occurring 30 days before through 180 days after initiating SGA treatment.[11] The results of this study may not be generalizable to the

national population as the Medicaid population is usually sicker than the commercially insured population.[11]

Very little information exists in the literature regarding the monitoring of metabolic parameters in the national population with commercial insurance treated in a primary care setting Most importantly, none of the studies to date have assessed the monitoring of body mass index (BMI) and blood pressure in adolescents on antipsychotics. The ADA/APA guidelines suggest that physicians need to do a careful review of baseline metabolic parameters before or as soon as initiating antipsychotic treatment.[5] None of the studies conducted in adolescents have assessed the monitoring of metabolic parameters prior to initiating antipsychotic treatment (baseline). Very little information exists regarding the predictors of regular monitoring of metabolic parameters in adolescents treated with SGAs. A study by Morrato et al. assessed the demographic and clinical predictors of monitoring of glucose and lipid testing in SGA treated children. The strongest predictors associated with monitoring glucose and lipid testing were having an emergency room department visit, multiple mental health comorbidities, office visit, and hospitalization.[11] The limitation of this study was that it did not include an untreated comparison group. Also, the predictors of BMI and blood pressure monitoring were not assessed in this study and the question whether antipsychotic use is associated with monitoring of metabolic parameters remained unanswered. It remains unknown whether demographic characteristics, insurance type, concomitant medication use, and baseline medical conditions in addition to antipsychotic use are associated with regular monitoring of metabolic parameters among adolescents.

The purpose of the current study was to assess the frequency of regular monitoring of metabolic parameters as recommended by ADA/APA guidelines in adolescents (12–19 years old) receiving second generation antipsychotics (SGA) compared to age and gender matched comparison group in a predominantly primary care setting. The rationale for including a healthy cohort in this study was to assess the frequency of metabolic monitoring patterns among healthy patients and compare those to the monitoring patterns among adolescents on antipsychotics in whom the monitoring is recommended. By including a healthy cohort we wanted to assess the incremental impact of antipsychotics on monitoring of metabolic parameters. The secondary purpose of the study was to assess if antipsychotic use along with demographic, medications or baseline medical conditions predicted regular monitoring of metabolic parameters among adolescents.

Methods

Data source

The General Electric (GE) Centricity electronic medical record (EMR) database was used for this study. The GE EMR database has data on approximately ten million patients. The GE EMR database is comprised of data submitted by more than 70 consortium member institutions located in more than 40 states. The GE Centricity is an EMR system that enables ambulatory care physicians and clinical staff to document patient encounters, streamline clinical workflow, and securely exchange clinical data with other providers, patients, and information systems. Centricity EMR is used by more than 20,000 clinicians to manage about 30 million patient records in 42 states, making it a

widely used ambulatory care EMR. This EMR system replaces the paper medical record for the patients in the participating medical offices. The EMR data are submitted voluntarily from physician groups across the country. A variety of practice types are represented ranging from solo practitioners to community clinics, to academic medical centers and large integrated delivery networks. The resulting research database provides information reflective of the clinical data captured in the practice setting, including diagnoses, chief complaints, medication orders, medication lists (patient-reported prescription and over-the-counter drug use), laboratory orders and results, and biometric readings. Data are collected centrally and go through a quality control process to clean the data and remove invalid values. The EMR database is deidentified and HIPAA compliant. Previous studies have used the GE EMR database in health outcomes studies.[12-14]

Study design

A retrospective cohort study design was used for this study. The retrospective cohort consisted of adolescents 12-19 years old. Within this cohort, adolescents with prescription for antipsychotics were considered the exposed group. The monitoring of this group was compared to what the guidelines recommend controlling for sporadic monitoring in the population by including the healthy comparison group.

Study population

Patients were eligible for inclusion in the exposure group if they 1) were 12–19 years old and, 2) had at least one prescription (index activity) for any SGA between January 2004 and July 2009 and, 3) had at least one documented physician visit ≥180 days before the index date and at least one documented physician visit 395 days after the index date and, 4) had no prescription for any antipsychotic agent during the 180 days before the index date (Figure 5). The comparison group in this study was selected from those without any antipsychotic medications. Patients in the comparison group were eligible for inclusion in this study if they 1) were 12–19 years old and, 2) had no prescription for any antipsychotic agent between January 2004 and July 2009 and, 3) had at least one documented physician visit ≥180 days before the index date and at least one documented physician visit 395 days after the index date. This was done to ensure that each patient had EMR data for at least 570 days (19 months) and to make sure that we were including patients who have healthcare coverage and are regularly visiting the physician during that time period. This methodology has been applied in previous publications based on the GE database.[12-14]

The date of patients' first prescription for any SGA after a pre index period of 180 days in the GE EMR database was selected as the index date for the exposed group. The antipsychotic drug prescribed on the index date was designated as the index drug. Patients were categorized as exposed to individual SGAs by their index drug. The follow-up period was 395 days from the index date.

Among the exposed individuals, analysis was limited to patients who remained on the one index antipsychotic drug throughout the follow-up period (monotherapy).

Stratified random sampling with 3:1 matching was used and the comparison group was matched to the exposed based on age, gender, and month of visit to the index antipsychotic prescription date.

Figure 6 provides the schematic of the study design. Electronic medical records for eligible patients were examined for presence of baseline and follow-up metabolic measurements such as BMI, blood pressure, total cholesterol, and fasting blood glucose levels. Metabolic measurements that occurred within 15 days before or after the index date were classified as baseline measurements. Fifteen days pre and postindex date was selected to allow one month for assessing baseline metabolic measurements. The guidelines mention that baseline measurements need to be assessed before initiating antipsychotic treatment or as soon as after initiating treatment. Therefore we used 15 days pre and post index date as a reasonable window for assessing baseline metabolic measurements. Metabolic measurements occurring within 16th day after the index date through the end of follow-up (index date + 395 days) were classified as follow-up measurements. A follow-up period of 395 days was used instead of 365 days to account for any gaps in therapy and to allow at least 30 days of follow-up period for antipsychotic prescriptions prescribed closest to the 365th day.

Demographic characteristics including age, gender, insurance type, and region were assessed during the 180 days preindex period. Insurance type and region were assessed to illustrate the baseline differences by insurance type and regional variation. Baseline medication use of beta blockers, oral antidiabetic agents associated with weight gain (such as human insulin, sulphonylureas, and thiazolidinediones) or loss (such as incretin mimetic agents and biguanides), antidepressants, anticonvulsants, and

corticosteroids that may influence metabolic monitoring was assessed during the 180 days preindex period. Baseline medical conditions such as dyslipidemia, hypertension, obesity, hypothyroidism, type 2 diabetes, bipolar disorder, schizophrenia, depression, and other mental illness that may influence metabolic monitoring were identified, using ICD-9 codes, in both the 180 days preindex and 395 days follow-up period. Newly diagnosed baseline medical conditions were defined as those conditions that were newly identified during the follow-up period for which there was no evidence in the preindex period.

The ADA/APA monitoring guidelines were used as a reference standard to categorize patients as being monitored regularly or irregularly for metabolic parameters.[15] According to the guidelines, BMI should be monitored at least 6 times during the one year follow-up period in addition to the baseline measurement. Fasting glucose and blood pressure should be monitored at least 2 times in the follow-up period in addition to having at least one baseline measurement. Lipid levels should be monitored at least 1 time in addition to having baseline measurement.. Based on these criteria, patients in the exposure and comparison group were categorized as being regularly monitored if the number of measurements was ≥7 for BMI, ≥3 for blood pressure, ≥2 for total cholesterol, and ≥3 for fasting blood glucose during the 395 days of follow-up period.

Analysis

Tests of proportions were used to evaluate differences between the antipsychotic group and comparison group in baseline demographics, baseline medications, baseline medical conditions, and frequency of baseline and regular monitoring of metabolic

parameters. Wilcoxon rank sum test was used to compare the mean number of metabolic measurements between the antipsychotic group and comparison group. Separate multivariate logistic regression analyses were conducted to assess the likelihood of regular monitoring of BMI and blood pressure. The frequency of monitoring of lipids and fasting blood glucose was extremely low, since they are done less frequently than blood pressure or BMI, for logistic regression modeling. To account for rare events, separate multivariate logistic regression for rare events was conducted to assess the likelihood of regular monitoring of total cholesterol and fasting blood glucose.[16, 17] The logistic regression for rare events uses methods with a lower mean square error thereby increasing the probability of an event. The regression analyses were conducted controlling for the individual SGAs, presence of baseline metabolic measurements, demographic characteristics, baseline medications, and baseline and newly diagnosed baseline medical conditions thought to be related to monitoring of metabolic parameters. All analyses were performed using STATA Version 10.0 (StataCorp. 2007. *Stata Statistical Software: Release 10*. College Station, TX: StataCorp LP). This study was approved by the institutional review board at the University of Utah on September 24th 2010.

Results

A total of 7,967 patients 12–19 years old with at least one prescription for a single type of SGAs were identified in the GE EMR database between the January 2004 and July 2009. Of these, the final sample consisted of 3,038 patients with at least one documented physician visit 180 days before the index date and at least one documented

physician visit 395 days after the index date. The comparison group consisted of 9,114 patients randomly matched to the exposure group. See Figure 5 for details of patient selection.

Table 5 provides the comparison of demographics, baseline medication use, and baseline medical conditions among patients in the exposure group and the matched comparison group. The mean age (15.53 years; SD, 2.22) and gender distribution (54% males) of patients in the exposure and comparison group was similar ($p>0.05$) as expected since matching was based on age and gender. A significantly higher percentage of exposed were from the South and Northeast US region while significantly higher percentage of the comparison group were from Midwest and West ($p<0.01$). The proportion of exposed with Medicare insurance was significantly higher than the comparison group ($p<0.01$). Patients in the exposure group had higher percentage of concurrent prescriptions for beta blockers, oral antidiabetic medications associated with weight loss, antidepressants, and anticonvulsants ($p<0.01$) while the comparison group had higher proportion on oral antidiabetic medications associated with weight gain, and corticosteroids ($p<0.01$) during the study period. The exposed had significantly higher proportion of baseline conditions including obesity, type 2 diabetes, and psychiatric conditions such as bipolar disorder, schizophrenia, depression, and other mental illness compared to the comparison group ($p<0.05$).

Frequency of baseline monitoring in the exposed and comparison group

Table 6 presents the frequency of baseline monitoring of metabolic parameters among adolescents on individual antipsychotics and the comparison group. If the guidelines were fully implemented, 100% of exposed patients would have baseline measures for each of the four metabolic parameters, but 0.63% of exposed patients had complete baseline monitoring. Patients on quetiapine had higher rates of baseline monitoring of BMI (51.7%), blood pressure (72.7%), total cholesterol (3.21%), and fasting blood glucose (4.59%) compared to the frequency of baseline monitoring of BMI (44.4%), blood pressure (62.6%), total cholesterol (1.8%), and fasting blood glucose (3.2%) in the comparison group. Patients on risperidone and olanzapine had higher rates of baseline monitoring of BMI (52.4% and 55.0%), blood pressure (58% and 74.4%), and fasting blood glucose (5.26% and 3.9%), respectively, compared to the comparison group. Patients on aripiprazole had higher baseline monitoring for BMI (52.2%) and total cholesterol (5.0%, $p<0.01$); and ziprasidone had higher frequency of monitoring for total cholesterol (9.8%, $p<0.05$) and fasting blood glucose compared to the comparison group.

Metabolic measurements in the exposed and comparison group

Table 7 presents the mean number of metabolic measurements among adolescents on individual antipsychotics and the comparison group during the one year follow-up period relative to the ADA/APA guideline recommendations. Adolescents on individual antipsychotics had lower mean number of metabolic measurement relative to those recommended by ADA/APA guidelines except for blood pressure where it was higher.

Adolescents on individual antipsychotics had significantly higher mean number of BMI, blood pressure, total cholesterol, and fasting blood glucose measurements compared to the group not prescribed SGAs ($p<0.01$).

Frequency of regular monitoring among the exposed and comparison group

There was evidence of adherence to monitoring for all metabolic parameters in the EMR for <1% of patients on antipsychotics. Regular monitoring of all four metabolic parameters as recommended by the ADA/APA guidelines was extremely low and not significantly different between the exposed and healthy comparison groups ($p>0.05$), except for patients on aripiprazole where the frequency was slightly higher ($p<0.01$). Table 8 presents the frequency of regular monitoring of metabolic parameters in adolescents on antipsychotics and the comparison group from 2004 to 2009. The frequency of regular monitoring of BMI and blood pressure was significantly higher among patients on individual antipsychotic agents such as aripiprazole (26.2% and 52.8%), olanzapine (23.3% and 62.2%), risperidone (24.9% and 49.0%), quetiapine (25.0% and 59.5%), and ziprasidone (29.2% and 54.9%) compared to the comparison group (9.5% and 37.4%, $p<0.01$), respectively. Similarly, the frequency of regular monitoring of total cholesterol (3.6%, 1.9%, 2.1%, 6.2%) and fasting blood glucose (1.6%, 1.4%, 1.7%, 4.4%) was significantly higher among adolescents on aripiprazole, risperidone, quetiapine, and ziprasidone respectively compared to the frequency of regular monitoring of total cholesterol (0.8%) and fasting blood (0.7%) in the comparison group ($p<0.05$). Adolescents on olanzapine had similar frequency of regular monitoring

of total cholesterol (p=0.478) but significantly higher frequency of regular monitoring of fasting blood glucose (2.3% vs. 0.7%) compared to the comparison group.

Predictors of BMI and blood pressure monitoring

Table 9 presents the predictors of regular monitoring of BMI and blood pressure. Antipsychotic treatment was a significant predictor of regular monitoring of BMI and blood pressure among adolescents. Patients on risperidone had the highest odds ratio of 2.65 followed by ziprasidone (OR: 2.62; 95% Confidence Interval [CI], 1.68–4.09), olanzapine (OR, 2.60; 95% CI, 1.89–3.57), aripiprazole (OR, 2.46; 95% CI, 1.89–3.57), and quetiapine (OR, 2.35; 95% CI, 1.98–2.80) for regular monitoring of BMI compared to the comparison group. Similar to BMI monitoring, being on antipsychotic treatment was significantly associated with higher likelihood of regular monitoring of blood pressure except for ziprasidone. Although statistically significant odds ratios were observed for regular monitoring of blood pressure, the likelihood of regular monitoring between the antipsychotic agents was not significantly different from each other because the confidence intervals for individual antipsychotics overlapped with each other. Compared to males, females were 1.52 and 1.44 times more likely to be regularly monitored for BMI and blood pressure, respectively. Patients on medications such as oral antidiabetic agents, corticosteroids, or with baseline medical conditions such as obesity, type 2 diabetes, and other mental illness were more likely to be regularly monitored for BMI and blood pressure. Given usual clinical practice, one might assume that adolescents are monitored for BMI and blood pressure at every physician office visit. According to the results, that may not be necessarily true for adolescents with dyslipidemia. Patients

with dyslipidemia were highly likely to be regularly monitored for blood pressure but this condition was not a significant predictor of monitoring BMI. Newly diagnosed baseline medical conditions such as dyslipidemia and type 2 diabetes significantly increased monitoring of BMI and blood pressure during the follow-up period. The proportion of case patients experiencing regular monitoring of BMI and blood pressure increased by 24% and 11% each year from 2004 to 2009, respectively, indicating an increase in the monitoring after the guidelines were published in 2004.

Predictors of lipid and glucose monitoring

Antipsychotic treatment was significantly associated with regular monitoring of total cholesterol and fasting blood glucose among adolescents. The likelihood of being regularly monitored for total cholesterol ranged from 2.48 (95% CI, 1.45–4.26) for risperidone, 2.52 (95% CI, 1.50–4.25) for quetiapine, 4.21 (95% CI, 2.50–7.08) for aripiprazole, and 7.34 (95% CI, 3.11–17.34) for ziprasidone compared to the comparison group. Statistically significant differences in odds were not observed for patients on olanzapine for regular monitoring of lipids but patients on olanzapine were 3 times more likely to be regularly monitored for fasting blood glucose compared to the comparison group. Also, patients on ziprasidone were 4 times more likely to be regularly monitored for fasting blood glucose. Adolescents on oral antidiabetic agents were associated with increased monitoring of total cholesterol and fasting blood glucose. Baseline diagnosis of dyslipidemia and newly diagnosed dyslipidemia were associated with increased monitoring of both total cholesterol and fasting blood glucose but only adolescents with newly diagnosed type 2 diabetes were associated with increased monitoring of fasting

blood glucose. The proportion of case patients experiencing regular monitoring of total cholesterol remained unchanged during the study period but regular monitoring of fasting blood glucose increased by 31% every year from 2004 to 2009.

Discussion

The GE EMR database used in this study is a predominantly primary care physician network database with a third of data representing care delivered by specialists. Therefore any trends observed in this data may be largely representative of primary care physicians practice. Primary care physicians are the first line of defense in diagnosing and treating psychiatric conditions. Many adolescents receive treatment from primary care physicians because of the dearth of child and adolescent psychiatrists. There is growing public health concern regarding the metabolic effects of these drugs in the adolescent population.[18, 19] The ADA/APA guidelines recommend regular monitoring of metabolic parameters in adolescents treated with antipsychotics. We assessed the frequency of regular monitoring of metabolic parameters as recommended by ADA/APA guidelines among adolescents with prescription for SGA compared to an untreated cohort in a predominantly primary care setting. Overall, 55% of the adolescents on antipsychotics were being regularly monitored for blood pressure, 25% for BMI, and approximately 2% for lipids and glucose compared to 9.46%, 7.43%, 0.76%, and 0.71%, respectively, in the comparison group as recommended by ADA/APA guidelines in this study. The frequency of regular monitoring observed in this study was higher for adolescents on antipsychotics than the untreated comparison group. However, the incremental difference in the frequency of monitoring among the exposed and unexposed

was extremely low. Specifically, the monitoring of lipids and glucose was less than 1% higher among adolescents with prescription for antipsychotics compared to the untreated cohort. Such low numbers are shocking in spite of the FDA requirement of adding warning to drug label stating the increased risk of hyperglycemia or diabetes associated with antipsychotics. The mean number of metabolic measurements and frequency of regular monitoring of metabolic parameters among adolescents on individual antipsychotic such as olanzapine, aripiprazole, risperidone, quetiapine, and ziprasidone did not appear to vary drastically even though olanzapine is associated with the highest risk of diabetes. Most importantly, less than 1% of exposed patients experienced monitoring of all four metabolic parameters as suggested by the guidelines which were not significantly different from the untreated comparison group. This study has demonstrated that relatively fewer numbers of adolescents with prescription for antipsychotics were being monitored regularly by clinicians who are treating them. Physicians need to be more proactive in monitoring to avoid the risk of development of dyslipidemia or diabetes among adolescents on antipsychotics. The reasons for the low monitoring of metabolic parameters could not be ascertained in this study and warrants further research.

The frequency of regular monitoring of lipids and glucose was extremely low as compared to other published studies. [11, 20] The frequency could be lower because this study's definition of regular monitoring was stringent compared to previous studies. We defined regular monitoring of metabolic parameters as recommended by ADA/APA guidelines within 1 year of initiating antipsychotic treatment while previous studies defined regular monitoring as at least one lipid or glucose measurement within 6 months

of antipsychotic prescription including the baseline lipid or glucose measurement. The ADA/APA guidelines provide the frequency of monitoring metabolic parameters within 1 year after the initiation of antipsychotic treatment and the current study was conducted to assess the frequency of monitoring of metabolic parameters as recommended by the guidelines. Also, previous studies have assessed monitoring patterns among Medicaid fee for service clients (6–17 years old) whereas this study assessed the frequency of metabolic monitoring in a predominantly primary care setting in a population that may be more generalizable as it contained patients with a variety of insurance types (commercial, Medicare, and Medicaid enrollees). [11, 20] Overall, the likelihood of monitoring metabolic parameters, as recommended by the ADA/APA guidelines published in February 2004, increased each year from the year 2004 onwards. Although, the frequency of monitoring of metabolic parameters is lower than expected, the results indicate that the guidelines are being put into practice gradually.

Antipsychotic treatment in adolescents was associated with increased monitoring of metabolic parameters. However, no differences were observed in the likelihood of regular monitoring of metabolic parameters across individual SGAs with the exception of fasting blood glucose. Adolescents on olanzapine or ziprasidone were being monitored regularly for fasting blood glucose while no differences were observed in the likelihood of regular monitoring among other SGAs compared to the comparison group. Even though antipsychotic treatment was associated with regular monitoring, the frequency of regular monitoring of metabolic parameters as recommended by ADA/APA guidelines among adolescents on antipsychotics was low.

The strongest predictors of regular monitoring of BMI were oral antidiabetic use and new diagnosis of type 2 diabetes. Both of these were stronger predictors of BMI monitoring than antipsychotic use. Adolescents with diagnosis of type 2 diabetes are encouraged to lose weight along with healthy eating and regular monitoring of blood glucose levels. Also, adolescents with type 2 diabetes may be visiting their primary care physician more often than others resulting in an increased monitoring of BMI compared to others. Preexisting and new diagnosis of dyslipidemia was found to be the strongest predictor of metabolic monitoring of blood pressure, total cholesterol, and fasting blood glucose with higher odds ratios than antipsychotic use. This finding is consistent with the results of the study by Haupt et al. conducted in adults.[8]

Although antipsychotic use was not the strongest predictor of metabolic monitoring, adolescents on antipsychotics with preexisting conditions had higher likelihood of metabolic monitoring compared to the comparison group with preexisting conditions. Adolescents on antipsychotics with preexisting chronic conditions such as diabetes and dyslipidemia may be monitored more regularly to manage the inherent chronic condition which may worsen because of the increased risk cardiometabolic adverse effects linked to antipsychotic treatment. However, the likelihood of regular monitoring among adolescents on antipsychotics without preexisting metabolic conditions was lower compared to those with preexisting conditions. Baseline diagnosis of obesity and mental illness associated with increased metabolic monitoring was consistent with previously published studies in children and adults.[8, 11, 20]

This study has several strengths. This study is the first to assess the monitoring patterns of metabolic parameters in adolescents (12–19 years old) using a predominantly

primary care large national electronic medical record database. Previous studies have been conducted in Medicaid population. Another strength of this study is that actual clinical measures such as BMI values, blood pressure readings, total cholesterol values, and fasting blood glucose levels in the GE EMR database were used to assess monitoring patterns in children and adolescents on antipsychotics. Previous studies have used current procedural terminology (CPT) codes and not actual clinical measures to assess monitoring patterns in children and adolescents on antipsychotics. [11, 20] As with any research study there are several limitations. One of the most important limitations of this study is that prescriptions in an EMR database are tracked by prescription orders and medication lists and not by actual prescriptions filled at the pharmacy. We cannot be entirely sure if patients are filling the prescriptions or taking prescriptions prescribed to them. Due to this limitation, misclassification of exposure may occur. Patients with at least one prescription order for an antipsychotic drug were considered to be on the drug during the follow-up period. This may result is misclassifying the patient as an antipsychotic user even if the patient is not actively or regularly taking the drug. Due to this limitation the results may be biased towards the null and attenuate the effect of antipsychotics on metabolic monitoring if one exists. Another limitation of the database is that it is predominantly primary care physician network database and, therefore, health care received outside of the primary care setting may not be captured in the database. This dataset likely includes antipsychotic users who are relatively less severe as compared to those patients seeking care from psychiatrists. As a result the results may be biased towards the null since we are automatically excluding sicker or more severe patients. However, an increasing number of primary care physicians are prescribing

antipsychotic drugs to children and almost 85% of all prescription for psychotropic medications are prescribed by primary care physicians and pediatricians.[21]

A significant limitation of the study is the missing BMI, lipids, blood glucose, and blood pressure values in the GE EMR database regardless of antipsychotic treatment. The foremost reason for missing values may be that the labs were not ordered by the primary care physician although results may not have been entered also. Another reason could be that the labs were ordered by other clinician than the primary care physician and never got entered into the GE database. This limitation may have resulted in a misclassification bias which was assumed to have been equally distributed between the antipsychotic group and the comparison group. Patients may have been misclassified as irregularly monitored when their clinical values were not included in the GE database due to above mentioned reasons. The direction of this bias is uncertain because we do not know the reason for missing values. The values can be actually missing (not monitored) or just missing from the database (in other words the patient is being monitored but values do not exist in the database). Future studies should validate the GE EMR data and identify the percentage of clinical values that were ordered but not entered in the database. Another limitation of this study is the lack of information on socioeconomic status, diet, physical activity, or overall health of patients' parents, which may directly or indirectly impact the monitoring of metabolic parameters in patients on antipsychotics in the GE EMR data.

Future studies should survey primary care providers to ascertain the challenges associated with monitoring of metabolic parameters among adolescents. Without regular monitoring of metabolic parameters, adolescents on antipsychotics are at higher risk of

growing into adulthood with abnormal weight and other metabolic parameters that impact adult obesity and its cardiovascular outcomes.[22-25] Strategies to improve awareness of ADA/APA guidelines and improve monitoring of metabolic parameters in adolescents on SGAs need to be developed.

Conclusions

Adolescents on antipsychotics are not being monitored according to guidelines published by the ADA/APA although their metabolic parameters are being monitored modestly more frequently than age and gender matched comparison group. In particular, the majority of adolescents treated with antipsychotics remain under monitored for BMI, lipids, and glucose as recommended by the ADA/APA guidelines. Antipsychotic users with preexisting and newly diagnosed metabolic conditions were most likely to be regularly monitored than antipsychotic users without such conditions. Without regular monitoring of metabolic parameters, adolescents on antipsychotics may be more likely to grow into adulthood with abnormal weight and other metabolic parameters and impact adult obesity and its cardiovascular outcomes. Strategies to increase awareness and adherence to ADA/APA guidelines in monitoring metabolic parameters among primary care physicians need to be developed. Clinicians need to be more proactive in monitoring metabolic parameters among all adolescents receiving antipsychotics prescriptions and not just those with preexisting metabolic conditions.

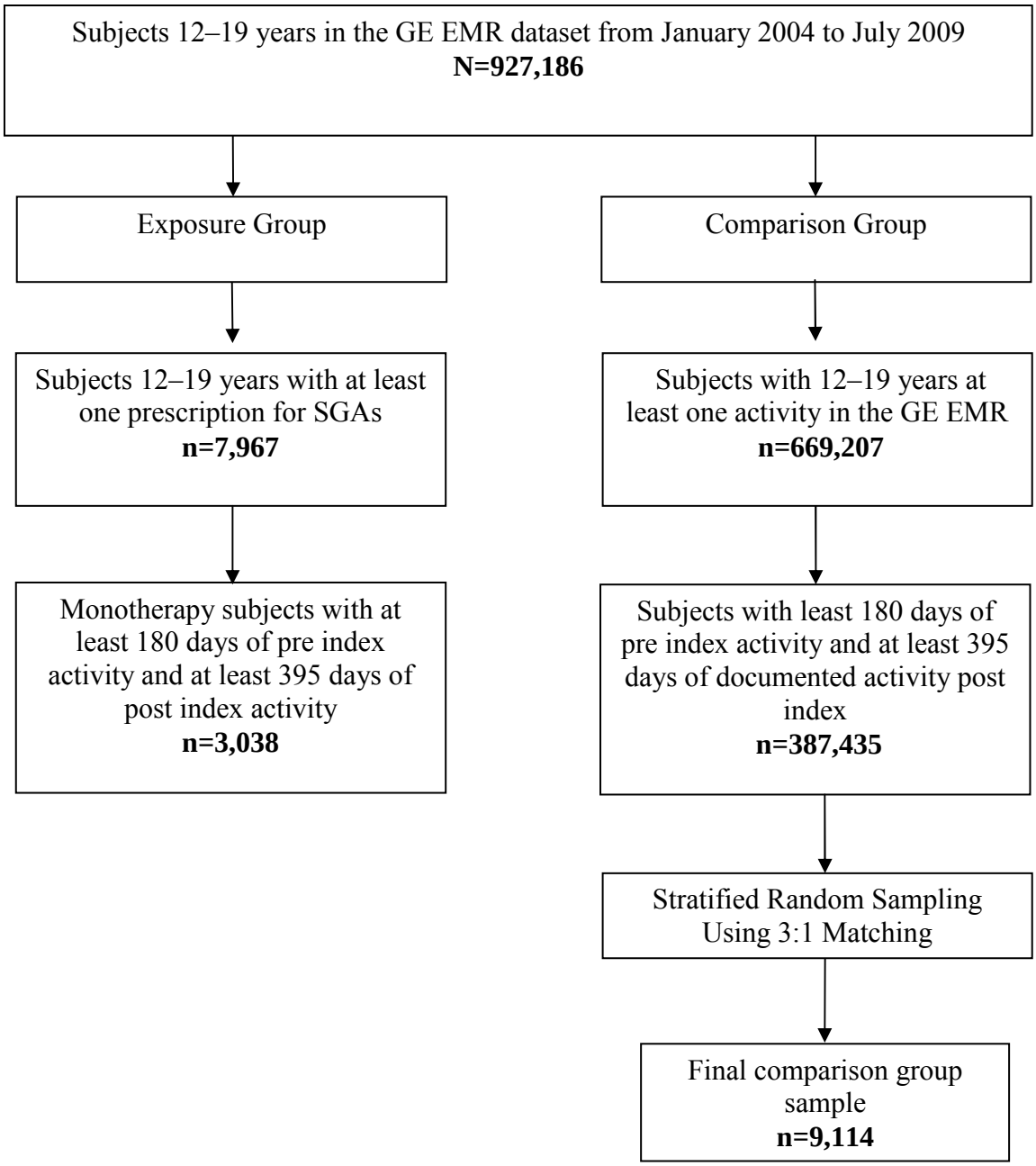

Figure 5 Flowchart of Patient Selection

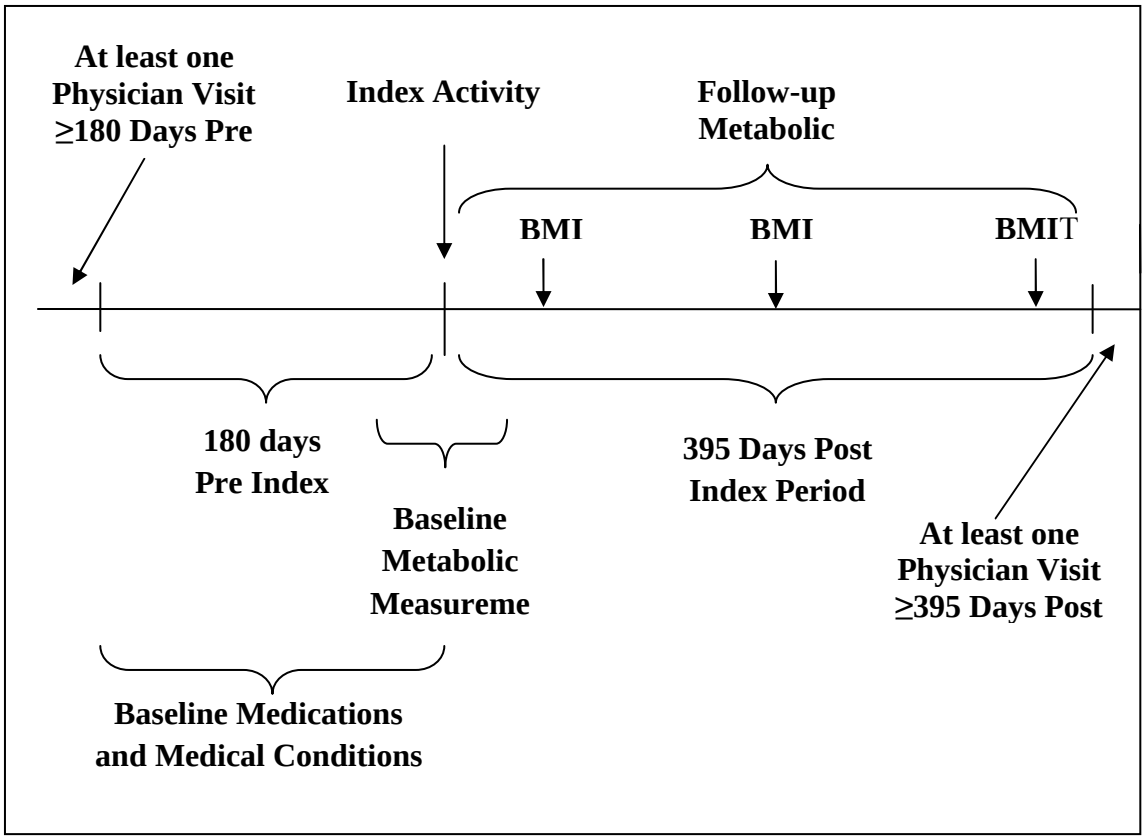

Figure 6 Schematic of Study Design

Table 5 Demographics, Medication Use, and Medical Conditions among Adolescents in Exposure and Comparison Group, 2004 to 2009

	Exposure Group n=3,038		Comparison Group n=9,114		P value
	n	%	n	%	
Age (Mean, SD)	15.53	2.22	15.53	2.22	1.000
Gender					
Males	1,647	54.21	4,941	54.21	1.000
Females	1,391	45.79	4,173	45.79	1.000
Race					
White	1,033	34.00	2,532	27.79	<0.001
Black	103	3.39	576	6.32	<0.001
Hispanic	39	1.28	273	3.00	<0.001
Other	35	1.15	140	1.54	0.124
Unknown	1,828	60.17	5,591	61.36	0.251
Region					
Northeast	729	24.00	1,899	20.84	<0.001
South	1,176	38.71	2,709	29.72	<0.001
Midwest	542	17.84	2,628	28.83	<0.001
West	591	19.45	1,878	20.61	0.172
Insurance Type					
Commercial	1,231	40.52	4,495	49.32	<0.001
Medicare	565	18.60	686	7.53	<0.001
Medicaid	48	1.58	19	0.21	<0.001
Self-pay	65	2.14	215	2.36	0.485
Other/Unknown	1,129	37.16	3,699	40.59	0.001
Baseline Medication Use					
Beta Blockers	38	1.25	27	0.3	<0.001
Antidiabetics Weight Gain	12	0.39	69	0.76	0.034
Antidiabetics Weight Loss	21	0.69	29	0.32	0.005
Antidepressants	56	1.84	38	0.42	<0.001
Anticonvulsants	297	9.78	66	0.72	<0.001
Corticosteroids	77	2.53	363	3.98	<0.001
Baseline Conditions					
Dyslipidemia	22	0.72	61	0.67	0.751
Hypertension	12	0.39	28	0.31	0.465
Obesity	111	3.65	170	1.87	<0.001
Hypothyroidism	12	0.39	20	0.22	0.102
Type 2 Diabetes	130	4.28	71	0.78	<0.001
Bipolar Disorder	361	11.88	23	0.25	<0.001
Schizophrenia	25	0.82	2	0.02	<0.001
Depression	119	3.92	25	0.27	<0.001
Mental Illness^	1,168	38.45	669	7.34	<0.001

^ Mental Illness was identified using ICD-9 codes 290 to 294 and 297 to 319

Table 6 Frequency of Baseline Monitoring of Metabolic Parameters among Adolescents in Exposure and Comparison Group, 2004 to 2009

	Total	Body Mass Index		Blood Pressure		Total Cholesterol		Fasting Blood Glucose	
		n	%	n	%	n	%	n	%
Comparison Group	9,114	4,047	44.40%	5,704	62.59%	166	1.82%	293	3.21%
Exposure Group (All SGAs)	3,038	1,582	52.07%	1,988	65.44%	91	3.00%	152	5.00%
Aripiprazole	642	335	52.18%	387*	60.28%	27	4.21%	32*	4.98%
Olanzapine	262	144	54.96%	195	74.43%	3*	1.15%	10	3.82%
Risperidone	931	488	52.42%	540	58.00%	21*	2.26%	49	5.26%
Quetiapine	1,090	563	51.65%	792	72.66%	35	3.21%	50	4.59%
Ziprasidone	113	52*	46.02%	74*	65.49%	5	4.42%	11	9.73%

*p>0.05, test of proportions was used to compare proportion of patients with baseline metabolic parameters on individual antipsychotic group to the comparison group.

Table 7 Mean Number of Metabolic Measurements among Adolescents on Antipsychotics Compared to Comparison Group Within One Year Relative to ADA/APA Recommendations

	Body Mass Index	**Blood Pressure**	**Total Cholesterol**	**Fasting Blood Glucose**
ADA/APA Guideline Recommendations	≥7	≥3	≥2	≥3
Comparison Group Mean (SD)	2.53 (3.28)	2.54 (3.28)	0.07 (0.33)	0.14 (0.60)
Exposure Group (All SGAs) Mean (SD)	4.74 (6.28)	3.86 (3.90)	0.17 (0.46)	0.27 (0.75)
Aripiprazole Mean (SD)	5.12 (6.56)	3.82 (4.13)	0.26 (0.54)	0.28 (0.71)
Olanzapine Mean (SD)	5.19 (8.25)	4.18 (4.00)	0.11 (0.36)	0.27 (0.74)
Risperidone Mean (SD)	4.49 (5.52)	3.33 (3.37)	0.16 (0.44)	0.26 (0.83)
Quetiapine Mean (SD)	4.64 (6.20)	4.23 (4.06)	0.14 (0.43)	0.25 (0.68)
Ziprasidone Mean (SD)	4.65 (6.04)	4.17 (4.20)	0.26 (0.60)	0.43 (0.90)

* Rank sum test was used and P value<0.01 for comparison of number of BMI, blood pressure, total cholesterol, and fasting blood glucose measurements among exposure group compared to comparison group and individual antipsychotic groups compared to comparison group.

Table 8 Frequency of Regular Monitoring of Metabolic Parameters as Recommended by ADA/APA Guidelines among Adolescents in Exposure and Comparison Group, 2004 to 2009

	Total	**Body Mass Index**		**Blood Pressure**		**Total Cholesterol**		**Fasting Blood Glucose**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Comparison **Group**	9,114	862	9.46%	3,411	37.43%	69	0.76%	65	0.71%
Exposure Group (All SGAs)	3,038	765	25.18%	1,668	54.90%	74	2.44%	53	1.74%
Aripiprazole	642	168	26.17%	339	52.80%	23	3.58%	10	1.56%
Olanzapine	262	61	23.28%	163	62.21%	3*	1.15%	6	2.29%
Risperidone	931	231	24.81%	456	48.98%	18	1.93%	13	1.40%
Quetiapine	1,090	272	24.95%	648	59.45%	23	2.11%	19	1.74%
Ziprasidone	113	33	29.20%	62	54.87%	7	6.19%	5	4.42%

*$p>0.05$, test of proportions was used to compare proportion of patients with baseline metabolic parameters on individual antipsychotic group to the comparison group.

Table 9 Adjusted Odds of Regular Monitoring of BMI, Blood Pressure, Total Cholesterol, and Fasting Blood Glucose among Exposed Adolescents Compared to the Comparison Group, 2004 to 2009

	BMI				Blood Pressure				Total Cholesterol				Fasting Blood Glucose			
	OR	**95% CI**		**P**	**OR**	**95% CI**		**P**	**OR**	**95% CI**		**P**	**OR**	**95% CI**		**P**
Age	0.97	0.94	0.99	**0.015**	1.07	1.05	1.09	**0.000**	1.04	0.96	1.12	0.305	1.04	0.95	1.15	0.360
Females (ref=Males)	1.52	1.36	1.70	**0.000**	1.44	1.33	1.55	**0.000**	0.63	0.43	0.92	**0.016**	1.27	0.85	1.89	0.239
Region (ref=Northeast)																
Southeast	1.47	1.27	1.71	**0.000**	0.86	0.78	0.96	**0.005**	0.74	0.48	1.13	0.161	0.95	0.56	1.62	0.855
Midwest	0.95	0.80	1.12	0.513	0.98	0.88	1.10	0.780	0.65	0.39	1.07	0.090	0.69	0.38	1.25	0.223
West	0.68	0.57	0.82	**0.000**	0.89	0.79	1.00	**0.042**	0.68	0.40	1.16	0.154	1.04	0.61	1.78	0.875
Insurance Type (ref=Commercial)																
Medicare	1.16	0.98	1.38	0.078	1.06	0.93	1.21	0.386	0.77	0.45	1.32	0.337	0.86	0.41	1.80	0.686
Medicaid	1.59	0.89	2.85	0.119	1.65	0.97	2.81	0.065	1.71	0.52	5.65	0.381	2.72	0.77	9.63	0.122
Self-pay	1.19	0.83	1.70	0.349	0.99	0.77	1.28	0.967	0.48	0.07	3.58	0.477	0.60	0.08	4.41	0.615
Other/Unknown	0.81	0.72	0.92	**0.001**	0.91	0.84	0.99	**0.021**	0.77	0.52	1.13	0.181	1.08	0.71	1.64	0.722
Treatment Group (ref= Comparison Group)																
Aripiprazole	2.46	2.00	3.04	**0.000**	1.53	1.28	1.82	**0.000**	4.21	2.50	7.08	**0.000**	1.53	0.72	3.24	0.271
Olanzapine	2.60	1.89	3.57	**0.000**	2.22	1.70	2.89	**0.000**	1.65	0.49	5.54	0.420	2.96	1.21	7.25	**0.018**
Risperidone	2.65	2.21	3.19	**0.000**	1.51	1.31	1.76	**0.000**	2.48	1.45	4.26	**0.001**	1.82	0.94	3.53	0.077
Quetiapine	2.35	1.98	2.80	**0.000**	1.88	1.63	2.16	**0.000**	2.52	1.50	4.25	**0.001**	1.78	0.99	3.17	0.052
Ziprasidone	2.62	1.68	4.09	**0.000**	1.41	0.95	2.09	0.085	7.34	3.11	17.34	**0.000**	4.26	1.33	13.65	**0.015**
Medications																
Beta Blockers	1.55	0.85	2.81	0.149	1.45	0.86	2.43	0.163	3.07	0.87	10.79	0.08	2.18	0.40	11.79	0.365
OAD Weight Gain	3.65	2.19	6.08	**0.000**	2.88	1.79	4.63	**0.000**	3.68	1.00	13.48	**0.049**	4.44	1.17	16.88	**0.029**
OAD Weight Loss	2.99	1.57	5.71	**0.001**	1.48	0.80	2.74	0.214	4.60	1.17	18.09	**0.029**	3.72	0.98	14.07	0.053
Antidepressants	1.57	0.97	2.55	0.068	1.31	0.85	2.01	0.223	1.49	0.34	6.50	0.597	1.64	0.34	7.86	0.539
Anticonvulsants	1.15	0.87	1.50	0.324	1.10	0.88	1.37	0.424	1.62	0.83	3.15	0.158	1.25	0.55	2.86	0.600
Corticosteroids	1.40	1.07	1.85	**0.016**	1.34	1.10	1.64	**0.004**	1.21	0.48	3.02	0.686	1.35	0.53	3.46	0.533
Baseline Conditions																
Dyslipidemia	1.12	0.60	2.08	0.731	1.60	1.01	2.52	**0.044**	9.78	4.15	23.03	**0.000**	7.83	2.95	20.78	**0.000**
Hypertension	1.89	0.86	4.14	0.115	1.43	0.72	2.85	0.306					0.65	0.03	15.12	0.787
Obesity	1.57	1.16	2.12	**0.003**	1.53	1.19	1.98	**0.001**	0.61	0.21	1.80	0.373	0.70	0.18	2.76	0.611
Hypothyroidism	1.38	0.57	3.32	0.471	0.95	0.45	1.97	0.885	1.67	0.27	10.24	0.578	1.72	0.19	15.73	0.630
Schizophrenia	0.93	0.36	2.41	0.884	0.94	0.43	2.07	0.881								
Bipolar Disorder	0.98	0.76	1.27	0.896	1.15	0.91	1.44	0.239	1.29	0.64	2.57	0.477	1.13	0.49	2.63	0.774
Depression	1.00	0.66	1.51	0.997	1.38	0.96	1.97	0.079	0.56	0.13	2.46	0.439	0.68	0.10	4.57	0.693
Type 2 Diabetes	1.84	1.32	2.55	**0.000**	1.36	1.00	1.85	**0.048**	0.90	0.31	2.63	0.852	1.03	0.37	2.86	0.949
Mental Illness^	1.52	1.32	1.75	**0.000**	1.52	1.36	1.70	**0.000**	0.98	0.64	1.50	0.931	1.42	0.90	2.25	0.133
Incident Conditions																
Dyslipidemia	2.16	1.38	3.39	**0.001**	3.17	2.02	4.98	**0.000**	11.85	6.09	23.05	**0.000**	7.81	3.62	16.86	**0.000**
Type 2 Diabetes	2.91	2.09	4.04	**0.000**	2.75	1.95	3.87	**0.000**	1.78	0.79	4.01	0.167	4.05	1.92	8.52	**0.000**
Year of Index Date	1.24	1.19	1.29	**0.000**	1.11	1.08	1.14	**0.000**	1.13	0.99	1.29	0.076	1.31	1.14	1.50	**0.000**

OR: Odds Ratio, P: P value, 95% CI: 95% Confidence Interval, ^ Mental Illness was identified using ICD-9 codes 290 to 294 and 297 to 319. The logistic regression analysis was adjusted for age, gender, insurance type, individual antipsychotic medications, baseline medications, baseline conditions, incident conditions, and year of index date.

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CHAPTER IV

ANTIPSYCHOTICS AND WEIGHT GAIN

Title: Association Between Second Generation Antipsychotics and Changes in Body Mass Index in Adolescents

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Abstract

Objective: To assess the association of second-generation antipsychotics (SGAs) prescriptions with changes in weight among adolescents compared to a matched, randomly selected age and gender untreated comparison group. **Methods:** A retrospective cohort study was conducted using the General Electric (GE) electronic medical record database between January 2004 and July 2009. Adolescents (12–19 years) with at least one prescription for any SGA and documented activity 540 days pre and 395 days post index were eligible for this study. Patients who were antipsychotic naïve (no evidence of antipsychotic prescription during 540 days pre index period) and monotherapy were eligible. The comparison group was stratified randomly matched (3:1) to the antipsychotic group based on age, gender, and month of antipsychotic prescription. Only those patients with at least one baseline BMI and follow up BMI 90 days post index date were eligible for inclusion. A maximum BMI during follow-up was evaluated and the percentage change in baseline to follow-up BMI was used as the outcome. Multivariate linear regression was used to assess the percent change in follow-up BMI from baseline among antipsychotic users compared to the comparison group controlling for covariates. **Results:** The mean age (15.35 years, SD 2.27) and gender (Males, 53%) distribution among the antipsychotic group (n=793) was similar ($p>0.05$) to the comparison group (n=2,373).. The mean percentage increase in BMI from baseline to follow-up for all patients with antipsychotic prescription was significantly higher than the comparison group ($p<0.01$) except for ziprasidone ($p>0.05$). Adolescents on olanzapine had the highest percentage increase in BMI from baseline to follow-up (5.84%, 95% Confidence Interval [CI], 4.07–7.61) followed by aripiprazole (4.36%; 95% CI, 3.08–

5.64), risperidone (3.65%; 95% CI, 2.61–4.68), and quetiapine (1.53%; 95% CI, 0.53–2.52) compared to the comparison group adjusting for covariates. **Conclusion:** Treatment with second generation antipsychotics is associated with significant increase in BMI among adolescents relative to a matched comparison group. Monitoring of weight is recommended among adolescents treated with antipsychotics.

Background

Second generation antipsychotics (SGAs), also known as atypical antipsychotics, are prescribed to adolescents in the United States as first line treatment for a variety of psychiatric and mood disorders, including but not limited to schizophrenia, bipolar disorder, and major depressive disorder.[1-4] The Food and Drug Administration (FDA) granted pediatric exclusivity for SGAs such as olanzapine, aripiprazole, and risperidone in 2007, while quetiapine was approved for pediatric use in 2009. Ziprasidone, another SGA, although without pediatric exclusivity is used off label in the pediatric population.[5] Published clinical trials have reported an increased risk of weight gain among both preadolescent and adolescent populations, as a result of SGAs.[6-9] Although clinical trials have addressed the issue of weight gain due to antipsychotic treatment, none have compared the individual SGAs to assess the differential impact of weight gain among adolescents.

A recent prospective cohort study conducted in 203 youths aged 4 to 19 years with 1 week or less of lifetime antipsychotic treatment assessed the association of SGA medications with body composition and metabolic parameters.[10] After a median of 10.8 weeks treatment with SGAs researchers reported that weight had increased by 8.5 kg

with olanzapine, by 6.1 kg with quetiapine, by 5.3kg with risperidone, and by 4.4 kg with aripiprazole compared with minimal weight change of 0.2 kg in the untreated comparison group.[10] Limitations of this study included the short duration of treatment (12 weeks), small comparison group (n=20), and limited generalizability of results to the national population. The study reported absolute change in body mass index (BMI) from baseline to 12 weeks of treatment without adjusting for or matching the comparison group to the treatment group by gender. Therefore the study does not account for the gender-related difference in BMI.

Another retrospective cohort study evaluated Medicaid medical and pharmacy claims to identify factors associated with incident cardiovascular events and metabolic disturbance in children and adolescents treated with antipsychotics.[11] The study found that antipsychotic treatment was associated with 2.13 times increased likelihood of obesity (odds ratio [OR], 2.13), compared to the untreated cohort.[11] One of the limitations of this study is the limited generalizability of the South Carolina's Medicaid enrollees to the US population as the Medicaid population is usually sicker than the commercially insured population.[12] The actual impact of antipsychotic treatment on clinical values was not known from this study.

There are limited retrospective comparative effectiveness studies comparing the differential risk of weight gain associated with SGAs in the adolescent population. The observational studies that have been conducted so far have either used short duration of treatment and a small comparison group or conducted studies that cannot be generalizable to the national population. A comparative effectiveness study that assesses the differential impact of SGAs on weight gain in adolescent population is warranted. The goal of the

current study is to compare the change in BMI among adolescents within 1 year of initiating antipsychotic treatment to the change in BMI among an age- and gender-matched, randomly selected, untreated comparison group.

Methods

Data source

The General Electric (GE) Centricity electronic medical record (EMR) database was used for this study. The GE EMR database includes approximately ten million patients and is comprised of data collected during routine use of the EMR by more than 70 consortium member institutions located in more than 40 states. The GE Centricity is an EMR system that enables ambulatory care physicians and clinical staff to document patient encounters, streamline clinical workflow, and securely exchange clinical data with other providers, patients, and information systems. Centricity EMR is used by more than 20,000 clinicians to manage about 30 million patient records in 42 states, making it a widely used ambulatory care EMR. This EMR system replaces the paper medical record for the patients in the participating medical offices. A variety of practice types are represented ranging from solo practitioners to community clinics, to academic medical centers, and large integrated delivery networks. The resulting research database provides information reflective of the clinical data captured in the practice setting, including diagnoses, chief complaints, medication orders, medication lists (patient-reported prescription and over-the-counter drug use), laboratory orders and results, and biometric readings. Data are collected centrally and go through a quality control process to clean

the data and remove invalid values. The EMR database is de-identified, HIPAA compliant and has been used in previous health outcomes studies.[13-15]

Study design

A retrospective cohort study design was used for this study. The retrospective cohort consisted of adolescents 12-19 years old. Within this cohort, adolescents with any prescription for second-generation antipsychotics were considered as the exposed group while nonprescribed adolescents were considered as the unexposed or the comparison group.

Study population

Patients in the exposure group were eligible for inclusion in this study if they 1) were 12–19 years old and, 2) had at least one prescription for any SGA between January 2004 and July 2009 and, 3) had at least one documented physician visit ≥540 days before the index date (defined below) and at least one documented physician visit ≥ 395 days after the index date and, and 4) had no prescription for any antipsychotic agent during the 540 days before the index date (Figure 1). Patients in the exposure group were assigned an index date which was their first prescription for antipsychotic medication and were categorized as exposed to individual SGAs depending on the type of their index antipsychotic prescription. We limited the analysis to antipsychotic naïve patients (i.e., no prescription during the pre index period of 540 days) to increase the chances of identifying fresh starts on antipsychotic treatment. Only those patients that received the

same antipsychotic agent as the index antipsychotic agent throughout the follow-up period, defined as monotherapy, were included in this study. Small proportions of exposed patients (10%) switched medications or were prescribed multiple antipsychotics during the follow up period and were excluded from this study.

The comparison population was identified based on presence of an activity (medical visit or prescription) in the GE EMR database and no prescriptions for any SGA. Patients in the comparison group were eligible for inclusion in this study if they 1) were 12–19 years old and, 2) had no prescription for any antipsychotic agent between January 2004 and July 2009 and, 3) had at least one documented physician visit ≥540 days before the index date and at least one documented physician visit ≥395 days after the index date.

Both the exposure and comparison group were followed for a period of 395 days from the date of index prescription or activity defined as the follow-up period. A follow-up period of 395 days was used to account for any gaps in therapy and to allow 30 days follow-up period for antipsychotic prescriptions prescribed closest to the 365th day. We restricted analysis to patients with a documented physician visit at least 540 days before index date and at least one documented physician visit 395 days after index date. This was done to ensure that patients were active participants in the healthcare system and were regularly visiting the physician during this period. This methodology has been applied in previous publications based on the GE database.[13-15] The final comparison group population consisted of individuals who were matched (3:1) to the antipsychotic group through a stratified, random sampling procedure based on age, gender, and month of activity.

The EMR was examined for the presence of baseline and follow up BMI measurements. Baseline BMI measurements were defined as those that occurred in the 30 days before the index date. BMI measurements that occurred 90 days post index date through the end of follow-up period were categorized as follow up measurements. Only those patients with baseline and at least one follow up BMI measurement were included in the analysis. An average of baseline values was taken if more than one existed during the 30-day period. Follow-up BMI measurements were categorized to each month depending on the date of BMI measurement and number of days from index date. An average of BMI values was taken if more than one BMI measurement was present in a particular month. The maximum BMI value during the follow-up period was identified and the mean difference and percentage change in baseline to maximum follow-up BMI was calculated. Excess weight for children and adolescents is defined based on the year 2000 CDC gender-specific BMI-for-age growth charts.[16] Children and adolescents with BMI <5th percentile are considered underweight, 5th to 85th percentile are normal weight, 85th to 95th percentile are considered overweight and those at and beyond the 95th percentile are considered obese.[17] Gender specific growth charts were used to categorize patients as underweight, normal weight, overweight, or obese at baseline and at follow-up.

Demographic characteristics such as age and gender, region, insurance type, medications, and baseline medical conditions were identified during the pre index period. Insurance type and geographic region (Northeast, Southeast, Midwest, and West) were identified to examine the baseline differences by insurance type and regional variation. Medications other than SGAs that may influence BMI such as beta blockers, oral

antidiabetic agents that cause weight gain (such as human insulin, sulphonylureas, and thiazolidinediones) or weight loss (such as incretin mimetic agents and biguanides), antidepressants, anticonvulsants, and corticosteroids were identified among all patients using prescription orders during the pre index period. Baseline medical conditions that may influence BMI such as dyslipidemia, hypertension, obesity, hypothyroidism, and type 2 diabetes; psychiatric conditions such as schizophrenia, depression, bipolar disorder, and other mental illness; and miscellaneous diagnosis were identified using ICD-9 codes during the pre index period. Mental illness encompassed psychoses, neurotic disorders, personality disorders, other nonpsychotic mental disorders, and mental retardation. Miscellaneous diagnoses included general symptoms, symptoms involving nervous and musculoskeletal systems, respiratory, head and neck, cardiovascular, digestive, urinary, nonspecific abnormal finding, and ill-defined and unknown causes of morbidity and mortality.

Analysis

Test of proportions was used to evaluate the differences in baseline demographics, baseline medications, and baseline medical conditions between the exposed and comparison groups. Student's t test with unequal variances was used to evaluate the differences in age, baseline BMI, maximum follow-up BMI, mean difference and percentage change in baseline to follow-up BMI between the exposed and comparison groups. Test of proportions was used to evaluate the differences in proportion of underweight, normal weight, overweight, and obese at baseline and follow-up. Multivariate linear regression analysis was conducted to assess the impact of SGA

exposure on percentage change in maximum follow-up BMI from baseline BMI controlling for demographic characteristics, baseline BMI, baseline medications, baseline baseline medical conditions, number of follow-up BMI measurements, number of months to maximum follow-up BMI, and year of index prescription. Analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC) and STATA Version 10.0 (StataCorp. 2007. *Stata Statistical Software: Release 10*. College Station, TX: StataCorp LP). This study was approved by the institutional review board at the University of Utah on September 24th 2010.

Results

A total of 7,967 adolescents with at least one prescription for SGAs and 669,207 adolescents without SGAs while were identified in the GE EMR database between January 2004 and July 2009 (Figure 7). Of those on SGAs, 3,039 patients had at least one documented physician visit ≥540 days before index date and at least one documented physician visit ≥395 days after index date. Of these, 2,295 patients had no evidence of antipsychotic prescription 540 days before index date and were on monotherapy during 395 days after index prescription. Of these, 1,731 patients had at least one baseline BMI in the 30 days prior to index antipsychotic prescription. The final exposed group consisted of 793 patients with at least one BMI recorded at 90 days or more following their index antipsychotic prescription. Of those without SGAs, 172,207 patients had at least one documented physician visit ≥540 days before index date and at least one documented physician visit ≥395 days after index date. Further, only those patients with at least one baseline BMI in 30 days prior and at least one follow-up BMI 90 days post

index date were included. The final comparison group consisted of 2,374 randomly selected patients matched to the antipsychotic group based on gender, age, and month of index antipsychotic prescription.

Demographics and medical conditions

Table 10 presents the demographics, medication use, and baseline medical conditions among the exposed and comparison group. The mean age (15.35 years; SD 2.27) and gender distribution (53% males) were similar among the antipsychotic group and the comparison group ($p>0.05$) which was as expected because of the matched selection strategy. The antipsychotic group had significantly higher proportion of patients from the Northeast, Southeast, Medicare, and Medicaid insurance ($p<0.01$). Also, the antipsychotic group had significantly higher proportion of patients with baseline medications, baseline medical conditions, psychiatric conditions, and other conditions ($p<0.05$).

Baseline and follow-up BMI values in exposed and comparison group

Table 11 presents the summary statistics for the baseline and follow-up BMI values among the comparison group, antipsychotic group, and antipsychotic group stratified by individual antipsychotic agents. Overall, the exposure group had significantly higher mean baseline BMI, follow-up BMI, mean difference, and percent change from baseline to follow-up BMI. The time in months to maximum BMI value was

significantly shorter, and the numbers of BMI measurements were greater in the exposed group compared to the group not prescribed SGAs.

Among the individual antipsychotic agents, the mean baseline BMI among patients on olanzapine and risperidone was similar to the comparison group ($p>0.05$). However, patients on ziprasidone, aripiprazole, and quetiapine had higher baseline BMI compared to the group not prescribed SGAs. Adolescents on individual antipsychotic agents had a significant percentage increase ($p<0.01$) in follow-up BMI from baseline except for patients prescribed ziprasidone where the percentage increase was not significant ($p=0.211$) compared to those not prescribed SGAs. Although, the baseline BMI in adolescents on olanzapine was similar to the comparison group the mean percentage increase from baseline to follow-up BMI was highest for patients prescribed olanzapine (8.50%). Adolescents on aripiprazole (7.88%), risperidone (7.34%), and quetiapine (5.02%) had relatively lesser percentage increase in baseline to follow up BMI than olanzapine but significantly higher compared to those not prescribed SGAs. BMI was measured more often in adolescents on individual antipsychotics with significantly higher mean number of BMI measurements ($p<0.01$) during the follow-up period except for olanzapine. The mean number of BMI measurement among adolescents on olanzapine was not statistically different from the comparison group. The time in months to required to attain maximum follow-up BMI was shorter ($p<0.01$) for adolescents on individual antipsychotic agents except for ziprasidone compared to those not prescribed SGAs.

Linear regression results

Table 12 presents the adjusted linear regression coefficients for percent change in BMI from baseline to follow-up among adolescents on individual antipsychotic agents compared to the group not prescribed SGAs adjusting for demographic characteristics, baseline medications, baseline medical conditions, year of index date, number of follow-up BMI measurements, and time in months to maximum follow-up BMI. Adolescents on olanzapine had the highest percentage increase in BMI during the 395-day follow-up period (5.84%, 95% confidence interval [CI], 4.07–7.61). Patients on aripiprazole had 4.36% (95% CI, 3.08–5.64) followed by risperidone (3.65%; 95% CI, 2.61–4.68), and quetiapine (1.53%; 95% CI, 0.53–2.52) compared to the comparison group. The small number of adolescents on ziprasidone did not show a statistically significant change in BMI.

Baseline BMI was significantly associated with percentage change in baseline to follow-up BMI. Although not statistically significant, adolescents who were underweight had a 1.2% increase in baseline to follow-up BMI compared to normal weight adolescents. However, adolescents who were normal weight gained more weight compared to overweight and obese adolescents. Normal weight adolescents had 0.96% increase in baseline to follow- up compared to overweight and 1.42% increase in follow-up BMI compared to obese adolescents. As age increased from 12 to 19 years the percentage change from baseline to follow-up BMI decreased by 0.33% for each year. Gender, region, insurance status, baseline medications, and baseline medical conditions were not significant predictors in the linear model.

Discussion

The purpose of the study was to assess the association of SGAs with changes in BMI among adolescents compared to a stratified random age and gender matched untreated comparison group. Prescription of olanzapine, aripiprazole, risperidone, and quetiapine was associated with significant changes in BMI after initiating antipsychotic treatment compared to the untreated comparison group. Only adolescents prescribed ziprasidone did not show significant changes in BMI compared to the untreated comparison group. This is likely due to the small sample size of patients on ziprasidone which may not be enough to detect a statistically significant difference. Patients prescribed quetiapine had the lowest percentage change in follow-up BMI from baseline BMI compared to the comparison group and those on other antipsychotics.

The results indicate that adolescents on antipsychotics gained more weight in a shorter duration of time compared to the comparison group. Adolescents on antipsychotics gained 7% of baseline BMI in 8 months of initiating antipsychotic treatment while the comparison group gained 3% of baseline BMI in 9 months. The results of this study were consistent with the previously discussed prospective cohort study where olanzapine, aripiprazole, risperidone, and quetiapine were associated with significant increases in weight among adolescents.[10]

The public health implications of adolescent patients on antipsychotic drugs and its associated cardiometabolic adverse effects are substantial. At present obesity is a serious health concern among all adolescents. Weight gain as a result of antipsychotic medications may cause further problems in these adolescents since their self-esteem may already be low due to coping with their mental illness and weight gain can make it worse.

Weight gain is not only an issue of self-esteem; it is also associated with long term health risks of obesity, type 2 diabetes, hyperlipidemia, and hypertension.[18] Children and adolescents who are obese are more likely to become obese adults. A study published by Whitaker et al. found that approximately 80% of children who were overweight at age 10–15 years were obese adults at age 25 years.[19] In addition, childhood obesity is associated with adult cardiovascular adverse outcomes and impaired glucose tolerance.[20-23] If weight gain among adolescents on antipsychotics is not controlled, it may result in high burden and increased use limited health resources to treat obesity-related diseases in addition to mental health issues when these adolescents become adults. Also, obesity and mental illness may result in serious consequences on the quality of life of adolescents.

Interestingly, normal weight adolescents on antipsychotics gained proportionally more during the follow-up period compared to the overweight and obese adolescents. Physicians may be more aggressively monitoring weight and taking steps to decrease weight gain in the overweight and obese adolescents on antipsychotics than their normal weight counterparts. It is important to monitor BMI systematically in overweight and obese adolescents on antipsychotics. However, it is equally important to monitor and control BMI in normal weight adolescents on antipsychotics using weight management strategies after initiating antipsychotic treatment to prevent transitioning from normal weight to overweight or obese.

The American Diabetes Association (ADA)/ American Psychiatric Association (APA) guidelines, published in February 2004, recommend monitoring of metabolic parameters such as weight and body mass index (BMI), blood pressure, fasting plasma glucose, and fasting lipid profile for all patients receiving antipsychotic treatment

regardless of age.[24] According to the guidelines, BMI should be monitored at least 4 times within 90 days and 3 times post 90 days of initiating antipsychotic treatment. In this study, adolescents on antipsychotics nearly met the guidelines for BMI monitoring with slightly less than 3 BMI measurements post 90 days of initiating antipsychotic treatment. The SGA group had significantly more BMI measurements compared to the group not prescribed SGA. There was heterogeneity by individual SGA, however. Adolescents prescribed olanzapine had the lowest number of BMI measurements among adolescents prescribed SGA. Their BMI monitoring was not significantly different from the untreated comparison group's even though olanzapine treatment is associated with the highest risk of weight gain and metabolic changes among the SGAs.[10] Physicians treating adolescents with antipsychotics need to be familiar with treatment guidelines and review the weight gain potential associated with antipsychotic agents and regularly monitor adolescents to avoid the long term risks.

In this study, almost half of the adolescents with prescription for SGAs were from the South US. This is consistent with previous studies where the proportion of overweight adolescents and children from the South was the highest.[25, 26] As expected, we observed a higher proportion of adolescents on antipsychotics had commercial insurance followed by Medicaid. Almost 55% of U.S. children have employer based health insurance while Medicaid along with other state programs cover 29% of U.S. children.[27] However, the proportion of adolescents with Medicaid insurance was significantly higher among antipsychotic users than nonantipsychotic users ($p<0.01$). Medicaid youths are 4 times as likely to be prescribed an antipsychotic compared to youths with commercial

insurance.[26-28] and antipsychotic prescribing has increased considerably in adolescents with Medicaid insurance.[28]

The primary strength of this study is that actual clinical measures such as BMI values in the GE EMR database were used to assess change in weight among adolescents on antipsychotics. Previous studies have used current ICD-9 codes and not actual clinical measures to assess obesity/weight gain in adolescents on antipsychotics[11] which may have resulted in reporting conservative estimates. ICD-9 codes for obesity are not frequently used, and patients who became obese after antipsychotic treatment may have been missed. Also, ICD-9 codes define obesity as BMI above 30kg/m^2 which may not apply to adolescents where overweight and obesity is defined based on BMI percentiles compiled on growth charts from the Centers for Disease Control and Prevention.[16] Another strength of the study is the use of a national population and age and gender matched stratified random comparison group. Previous study has reported absolute change in body mass index (BMI) without adjusting for or matching the comparison group to the treatment group by gender and therefore did not account for gender-related differences in BMI.

As with any research study there are several limitations. One of the most important limitations of this study is that prescriptions in an EMR database are tracked by prescription orders and medication lists and not by actual prescriptions filled at the pharmacy. We cannot be entirely sure if patients are filling and taking medications prescribed to them. Due to this limitation misclassification of exposure may occur. Patients with at least one prescription order for a SGA were considered to be on the drug during the follow up period. This may have resulted in misclassifying patients as

antipsychotic users even if the drug was not taken throughout the follow up period and creating a bias toward no effect of the drug upon weight. Another limitation of the database is that it is predominantly a primary care physician network and, therefore, health care received outside of the primary care setting may not be captured in the database. We are probably studying antipsychotic users who are relatively less sick compared to those patients seeking care from psychiatrists. However, an increasing number of primary care physicians are prescribing antipsychotic drugs to children on the front line when it comes to diagnosing and treating mental disorders. Almost 85% of all prescription for psychotropic medications are prescribed by primary care physicians and pediatricians.[29]

Missing BMI values in the GE EMR database are another limitation for this study, but we have no evidence that inclusion of BMI values are associated with SGA prescription and assume that the bias is nondifferential. Another limitation of this study is that the comparison group was identified based on their index activity in the GE EMR database. This may have resulted in a selection bias and the comparison group patients may be monitored more often during their initial visits to the physician. However, a 6-month preindex period was used which may have accounted for this bias. Finally, the database lacks information on socioeconomic status, diet, physical activity, or overall health of patient's parents. These unmeasured variables, among other variables, play a significant role in impacting the weight of adolescents in the data.

A small proportion of patients on antipsychotics (10%) switched medications or were on multiple antipsychotics in this study. Adolescents on antipsychotics in predominantly primary care setting may be less severe and better managed on a single

antipsychotic agent. Due to small sample size, this group was excluded from the analysis and may have resulted in conservative estimates being presented in this study.

Conclusions

Second generation antipsychotic treatment in adolescents is associated with significant increase in BMI relative to a matched comparison group. Aggressive monitoring of weight is recommended among adolescents treated with antipsychotics and promoted in professional treatment guidelines such as those from the ADA/APA.

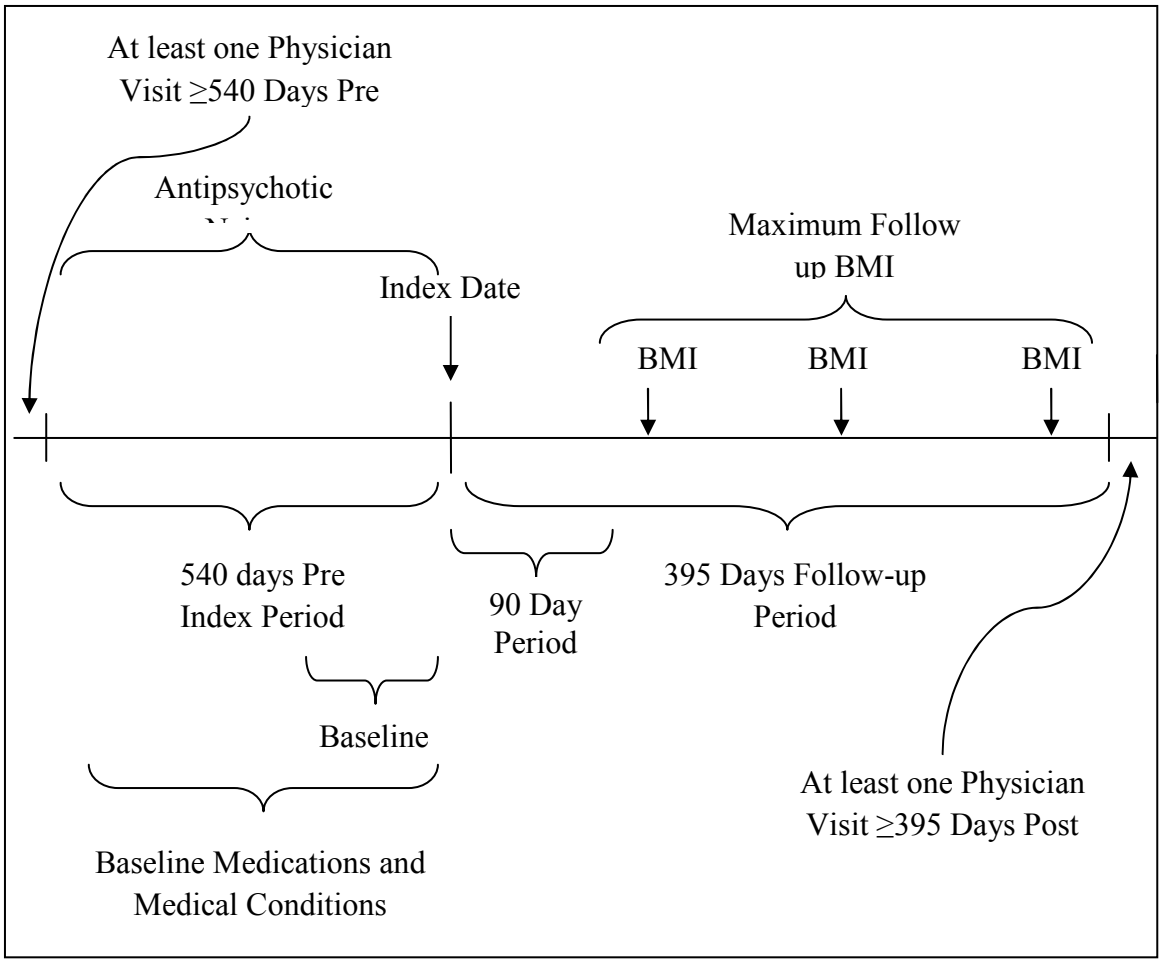

***Figure not drawn to scale**

Figure 7 Schematic of Study Design

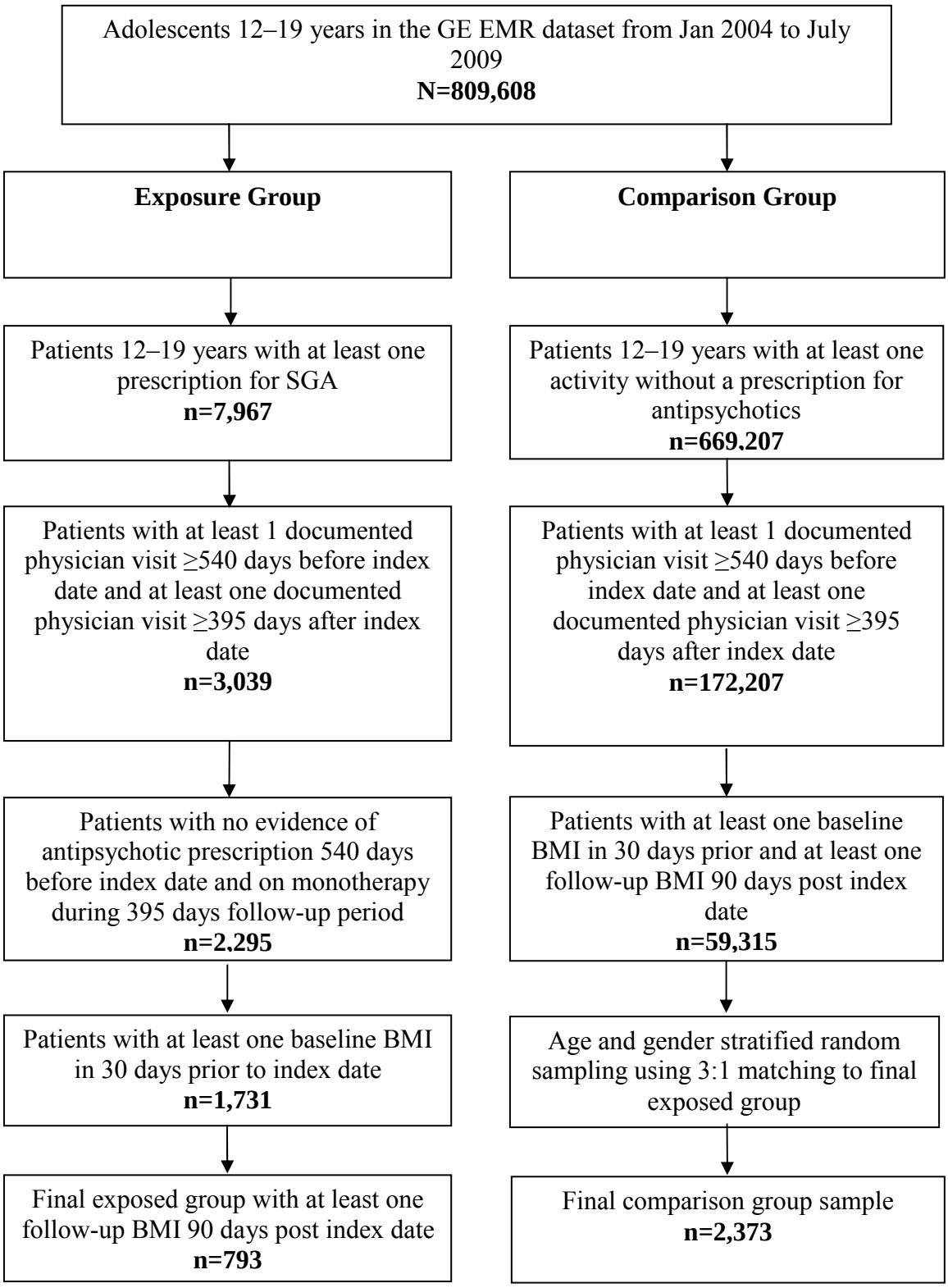

Figure 8 Flowchart of Patient Selection

Table 10 Demographics, Medication Use, and Medical Conditions in Exposed and Comparison Group Adolescents, 2004 to 2009

	Comparison Group n=2,373		**Exposure Group n=793**		**P Value**
	n	**%**	**n**	**%**	
Mean Age (SD)	15.35 (2.27)		15.35 (2.28)		0.928
Gender					
Males	1248	52.59	418	52.71	0.953
Females	1125	47.41	375	47.29	0.953
Region					
Northeast	436	18.37	197	24.84	<0.001
Southeast	823	34.68	371	46.78	0.006
Midwest	453	19.09	117	14.75	<0.001
West	661	27.86	108	13.62	<0.001
Insurance Type					
Commercial	1159	48.84	370	46.66	0.287
Medicaid	119	5.01	145	18.28	<0.001
Medicare	3	0.13	10	1.26	<0.001
Self-pay	46	1.94	12	1.51	0.440
Other/Unknown	1046	44.08	256	32.28	<0.001
Baseline Medications					
Beta Blockers	0	0.00	14	1.77	<0.001
Oral Antidiabetics	3	0.13	15	1.89	<0.001
Antidepressants	2	0.08	30	3.78	<0.001
Anticonvulsants	0	0	62	7.82	<0.001
Corticosteroids	17	0.72	59	7.44	<0.001
Baseline Medical Conditions					
Dyslipidemia	25	1.05	13	1.64	0.190
Hypertension	4	0.17	6	0.76	0.011
Obesity	72	3.03	63	7.94	0.011
Hypothyroidism	6	0.25	8	1.01	<0.001
Psychiatric Conditions					
Schizophrenia	0	0.00	4	0.50	<0.001
Bipolar Disorder	9	0.38	66	8.32	<0.001
Depression	4	0.17	31	3.91	<0.001
Type 2 Diabetes	7	0.29	56	7.06	<0.001
Other Conditions					
Miscellaneous Diagnosis*	285	12.01	299	37.70	0.000
Mental Illness^	167	7.04	379	47.79	0.000

*Miscellaneous Diagnosis consists of ICD-9 codes 780 to 799, ^ Mental Illness was identified using ICD-9 codes 290 to 294 and 297 to 319

Table 11 Summary Statistics for Baseline and Follow up BMI Values among Exposed and Comparison Group Adolescents, 2004 to 2009

	Comparison Group N=2,373		**Antipsychotic Group N=793**		**Antipsychotic Group N=793**									
					Aripiprazole N= 158		**Olanzapine N=74**		**Risperidone N=255**		**Quetiapine N=286**		**Ziprasidone N= 20**	
	N	N%	N	N%	N	N%	N	N%	N	N%	N	N%	N	N%
Mean Baseline BMI (SD)	23.81 (5.23)		24.68 (6.41)^		26.09 (6.88)^		24.51 (6.15)		23.21 (5.80)		24.95 (6.35)^		29.08 (7.32)^	
Underweight [a]	40	1.69	29	3.66^	2	1.27	6	8.11^	11	4.31^	10	3.50*	0	0.00
Normal Weight [b]	1,473	62.07	429	54.1^	78	49.37^	40	54.05	150	58.82	154	53.85^	7	35.00*
Overweight [c]	407	17.15	123	15.51	18	11.39	11	14.86	44	17.25	48	16.78	2	10.00
Obese [d]	453	19.09	212	26.73^	60	37.97^	17	22.97	50	19.61	74	25.87^	11	55.00^
Mean Follow-up BMI (SD)	24.57 (5.44)		26.25 (6.88) ^		28.01 (7.29)^		26.60 (7.09)^		24.82 (6.13)		26.20 (6.95)^		29.93 (6.94)^	
Underweight	19	0.8	14	1.77^	2	1.27	3	4.05^	1	0.39	8	2.80^	0	0.00
Normal Weight	1,362	57.4	375	47.29^	61	38.61^	33	44.59*	135	52.94	141	49.30^	5	25.00^
Overweight	468	19.72	140	17.65	22	13.92	15	20.27	55	21.57	44	15.38	4	20.00
Obese	524	22.08	264	33.29^	73	46.20^	23	31.08	64	25.10	93	32.52	11	55.00^
Mean Difference (Baseline to Max Follow-up BMI) (SD)	0.76(1.72)		1.57(2.26) ^		1.93(2.68)^		2.09 (2.42)^		1.61 (2.03)^		1.25 (2.04)^		0.85 (2.95)	
Mean Percentage Increase (Baseline to Max Follow-up BMI) (SD)	3.40 (6.95)		6.63 (9.07)^		7.88 (10.40)^		8.50 (9.57)^		7.34 (9.03)^		5.02 (7.69)^		3.97 (11.25)	
Mean Follow-up time to Max BMI (months) (SD)	8.83 (2.39)		7.99 (2.92)^		7.99 (2.98)^		7.55 (3.04)^		8.17 (2.88)^		7.93 (2.85)^		8.00 (3.58)	
Mean No. of BMI Measurements Post 90 Days Index Rx (SD)	2.08 (1.34)		2.70 (1.71)^		2.96 (1.87)^		2.35 (1.74)		2.47 (1.45)^		2.83 (1.77) ^		3.00 (2.15)^	

^p<0.01, *p<0.05. Test of proportions were used to compare the individual antipsychotics to the comparison group. [a] Underweight: BMI<5th Percentile; [b] Normal Weight: BMI ≥5th to <85th Percentile; [c] Overweight: BMI ≥85th to <95th Percentile; [d] Obese; BMI ≥95th Percentile

Table 12 Adjusted Linear Regression Coefficients for Percentage Change in Baseline to Maximum Follow-up BMI in Adolescents from 2004 to 2009

	Adjusted Coefficients*	95% CI		P value
Baseline BMI				
Normal Weight (<85th Percentile)	***ref***			
Underweight (<5th Percentile)	1.20	-0.57	2.96	0.184
Overweight (≥85th to <95th Percentile)	-0.95	-1.65	-0.24	0.008
Obese (≥95th Percentile)	-1.41	-2.07	-0.74	<0.001
Treatment				
Comparison Group	***ref***			
Aripiprazole	4.36	3.08	5.64	<0.001
Olanzapine	5.84	4.07	7.61	<0.001
Risperidone	3.65	2.61	4.68	<0.001
Quetiapine	1.53	0.53	2.52	0.003
Ziprasidone	0.99	-2.32	4.30	0.559
Gender				
Males	***ref***			
Females	-0.25	-0.78	0.29	0.364
Age in Years	-0.33	-0.45	-0.21	<0.001
Region				
Northeast	***ref***			
Midwest	0.16	-0.56	0.88	0.664
South	-0.29	-1.13	0.55	0.501
West	-0.09	-0.88	0.71	0.828
Insurance				
Commercial	***ref***			
Medicaid	-0.65	-1.62	0.33	0.194
Medicare	-3.37	-7.42	0.68	0.103
Self Pay	-0.37	-2.29	1.56	0.710
Unknown	0.18	-0.39	0.75	0.535

*Adjusted for baseline medications, baseline medical conditions, psychiatric conditions, other conditions, number of follow-up BMI values, year of index prescription or activity, and number of months to maximum follow-up BMI.

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CHAPTER V

CONCLUSIONS

The purpose of the study described in Chapter II was to assess the overall and quarterly trends of prevalence of overweight and obesity in adolescents on antipsychotics compared to a stratified random matched comparison group from 2000 to 2009. The hypothesis of this study was that increase in the prevalence of antipsychotic use increases the prevalence of overweight among adolescents on antipsychotics compared to those not treated with antipsychotics overall and across time. Overall, the prevalence of overweight and obese from 2000 to 2009 was found to be higher among male and female antipsychotic users compared to the male and female comparison group, respectively. However, the trend of overweight and obese adolescent male antipsychotic users decreased while the trend of overweight and obese nonantipsychotic user males increased from 2000 to 2009. The decreasing trend in male antipsychotic users may be associated with better management of excessive weight gain or use of antipsychotics with lower potential for weight gain or related to hormonal differences among male and female adolescents. Contrary to males, the trend in the prevalence of overweight and obese in female antipsychotic users increased while the trends for nonantipsychotic user females

remained unchanged from 2000 to 2009. The trend of prevalence of overweight and obese among the female comparison group remained stable and did not show statistically significant change. Antipsychotic treatment may have differential impact on weight gain in adolescent males and females or a disparity in monitoring metabolic parameters may exist between adolescent males and females. More research is needed that assesses the weight gain potential of antipsychotic treatment among adolescent males and females separately. Also, future studies should assess the monitoring patterns of metabolic parameters in adolescents treated with antipsychotics to assess if any disparity exists in monitoring metabolic parameters among males and females. The public health implications of overweight and obesity among children and adolescents in the United States are significant. Weight gain among adolescents may be associated with long term health risks of obesity, dyslipidemia, diabetes, and hypertension. If weight gain among adolescents on antipsychotics is not controlled, it may result in high burden and increased use of limited health resources to treat obesity-related diseases in addition to mental health issues when these adolescents become adults.

The ADA/APA guidelines recommend regular monitoring of metabolic parameters in adolescents treated with antipsychotics. In the study described in Chapter III we assessed the frequency of regular monitoring of metabolic parameters as recommended by ADA/APA guidelines among adolescents with prescription for SGA compared to an untreated cohort in a predominantly primary care setting. Also, based on the conclusion from study in Chapter II we wanted to assess if a disparity in monitoring metabolic parameters exists between adolescent males and females. Overall, 55% of the adolescents on antipsychotics were being regularly monitored for blood pressure, 25% for

BMI, and approximately 2% for lipids and glucose compared to 9.46%, 7.43%, 0.76%, and 0.71% respectively in the comparison group as recommended by ADA/APA guidelines in this study. The frequency of regular monitoring observed in this study was higher for adolescents on antipsychotics than the untreated comparison group. However, the incremental difference in the frequency of monitoring among the exposed and unexposed was extremely low. Specifically, the monitoring of lipids and glucose was less than 1% higher among adolescents with prescription for antipsychotics compared to the untreated cohort. Most importantly, less than 1% of exposed patients experienced monitoring of all four metabolic parameters as suggested by the guidelines which were not significantly different than the untreated comparison group. This study demonstrated that relatively fewer numbers of adolescents with prescription for antipsychotics were being monitored regularly by clinicians who are treating them. Overall, the likelihood of monitoring metabolic parameters, as recommended by the ADA/APA guidelines published in February 2004, increased each year from the year 2004 onwards. Although, the frequency of monitoring of metabolic parameters is lower than expected, the results indicate that the guidelines were being put into practice gradually. Antipsychotic treatment in adolescents was associated with increased monitoring of metabolic parameters. However, no differences were observed in the likelihood of regular monitoring of metabolic parameters across individual SGAs with the exception of fasting blood glucose. Adolescents on olanzapine or ziprasidone were being monitored regularly for fasting blood glucose while no differences were observed in the likelihood of regular monitoring among other SGAs compared to the comparison group. Even though antipsychotic treatment was associated with regular monitoring, the frequency of regular

monitoring of metabolic parameters as recommended by ADA/APA guidelines among adolescents on antipsychotics was low. Also, the likelihood of metabolic monitoring among females was higher and lower in some instances compared to males. The strongest predictors of regular monitoring of BMI were oral antidiabetic use and new diagnosis of type 2 diabetes. Both of these were stronger predictors of BMI monitoring than antipsychotic use. Preexisting and new diagnosis of dyslipidemia was found to be the strongest predictor of metabolic monitoring of blood pressure, total cholesterol, and fasting blood glucose with higher likelihood of regular monitoring than antipsychotic use. Although antipsychotic use was not the strongest predictor of metabolic monitoring, adolescents on antipsychotics with preexisting conditions had higher likelihood of metabolic monitoring compared to the comparison group with preexisting conditions. However, the likelihood of regular monitoring among adolescents on antipsychotics without preexisting metabolic conditions was lower compared to those with preexisting conditions. Adolescents on antipsychotics are not being monitored according to guidelines published by the ADA/APA although their metabolic parameters are being monitored modestly more frequently than age and gender matched comparison group. In particular, the majority of adolescents treated with antipsychotics remain under monitored for BMI, lipids, and glucose as recommended by the ADA/APA guidelines. Antipsychotic users with preexisting and newly diagnosed metabolic conditions were most likely to be regularly monitored than antipsychotic users without such conditions. Without regular monitoring of metabolic parameters, adolescents on antipsychotics may be more likely to grow into adulthood with abnormal weight and other metabolic parameters and impact adult obesity and its cardiovascular outcomes. Strategies to

increase awareness and adherence to ADA/APA guidelines in monitoring metabolic parameters among primary care physicians need to be developed. Clinicians need to be more proactive in monitoring metabolic parameters among all adolescents receiving antipsychotics prescriptions and not just those with preexisting metabolic conditions. Future studies should survey primary care providers to ascertain the challenges associated with monitoring of metabolic parameters among adolescents.

The purpose of the study described in Chapter IV was to assess the association of SGAs with changes in BMI among adolescents compared to a stratified random age and gender matched untreated comparison group. Prescription of olanzapine, aripiprazole, risperidone, and quetiapine was associated with significant changes in BMI after initiating antipsychotic treatment compared to the untreated comparison group. Only adolescents prescribed ziprasidone did not show significant changes in BMI compared to the untreated comparison group. Patients prescribed quetiapine had the lowest percentage change in follow-up BMI from baseline BMI compared to the comparison group and those on other antipsychotics. The results indicate that adolescents on antipsychotics gained more weight in a shorter duration of time compared to the comparison group. Adolescents on antipsychotics gained 7% of baseline BMI in 8 months of initiating antipsychotic treatment while the comparison group gained 3% of baseline BMI in 9 months. Interestingly, normal weight adolescents on antipsychotics gained proportionally more during the follow-up period compared to the overweight and obese adolescents. In this study, adolescents on antipsychotics nearly met the ADA/APA guidelines for BMI monitoring with slightly less than 3 BMI measurements post 90 days of initiating antipsychotic treatment. The SGA group had significantly more BMI measurements

compared to the group not prescribed SGA. There was heterogeneity by individual SGA, however. Adolescents prescribed olanzapine had the lowest number of BMI measurements among adolescents prescribed SGA. Their BMI monitoring was not significantly different from the untreated comparison groups even though olanzapine treatment is associated with the highest risk of weight gain and metabolic changes among the SGAs. In this study, almost half of the adolescents with prescription for SGAs were from the South US. As expected, we observed a higher proportion of adolescents on antipsychotics had commercial insurance followed by Medicaid. Second generation antipsychotic treatment in adolescents is associated with significant increase in BMI relative to a matched comparison group. Aggressive monitoring of weight is recommended among adolescents treated with antipsychotics and promoted in professional treatment guidelines such as those from the ADA/APA. The public health implications of adolescent patients on antipsychotic drugs and its associated cardiometabolic adverse effects are substantial. At present obesity is a serious health concern among all adolescents. Weight gain as a result of antipsychotic medications may cause further problems in these adolescents since their self-esteem may already be low due to coping with their mental illness and weight gain can make it worse. If weight gain among adolescents on antipsychotics is not controlled, it may result in high burden and increased use limited health resources to treat obesity-related diseases in addition to mental health issues when these adolescents become adults. Also, obesity and mental illness may result in serious consequences on the quality of life of adolescents.

In conclusion, the likelihood of metabolic monitoring among females was higher and lower in some instances compared to males and no significant differences in weight

gain were found after initiating antipsychotic treatment between adolescent males and females. This study was not able to assess if disparity in monitoring metabolic parameters existed between males and females. Future research should focus on metabolic monitoring in males and females on antipsychotics to assess if any disparity exists in monitoring metabolic parameters between males and females. In the current study we were only able to assess few predictors of metabolic monitoring among adolescents on antipsychotics due to limitations of the dataset used. This study was not able to determine the reasons for low monitoring of metabolic parameters among adolescents. Future studies should focus on determining the reasons for low monitoring by surveying primary care providers to ascertain the challenges associated with monitoring of metabolic parameters among adolescents. Without regular monitoring of metabolic parameters, adolescents on antipsychotics are at higher risk of growing into adulthood with abnormal weight and other metabolic parameters that impact adult obesity and its cardiovascular outcomes. More research is needed that assesses the weight gain potential of antipsychotic treatment among adolescent males and females separately.